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(54) Title: THERAPEUTIC APPLICATIONS OF T-BAM (CD40L) TECHNOLOGY TO TREAT INFLAMMATORY KIDNEY DISEASES

(57) Abstract

Activation by CD40 ligand of renal cells bearing CD40 on the cell surface is inhibited, both in vivo and ex vivo, with an agent capable of inhibiting interaction between CD40 ligand and CD40 on the cells. Inflammatory kidney diseases are treated.

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THERAPEUTIC APPLICATIONS OF T-BAM (CD40L) TECHNOLOGY TO TREAT INFLAMMATORY KIDNEY DISEASES

This application claims the priority of U.S. Serial No. 08/641,473, filed May 1, 1996 and U.S. Serial No. 08/587,334, filed January 16, 1996, the contents of which are hereby incorporated by reference.

The invention disclosed herein was made with Government support under NIH Grant Nos. K08-AR-01904, RO1-CA55713, RO1-AI-28367, RO1-AI-14969, HL21006, HL42833, HL50629, and RO1-AI-14969 from the Department of Health and Human Services. Accordingly, the U.S. Government has certain rights in this invention.

Throughout this application, various references are referred to within parentheses. Disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains. Full bibliographic citation for these references may be found in the text.

Background of the Invention

Immune complex deposition is known to play important roles in mediating the immunopathogenesis of a variety of renal diseases, including the glomerulonephritis associated with systemic lupus erythematosus. However, infiltrating renal interstitial leukocytes, predominately T cells and monocytes, are often seen in lupus nephritis and other inflammatory renal diseases. The precise role of infiltrating T cells in the inflammatory renal process that ultimately may result in renal scarring and end-organ damage is currently unknown. It is of interest that the extent of mononuclear cell infiltrate correlates with progression to renal failure. Some evidence

suggests that interstitial T cells play direct immunopathogenic roles in the initiation and/or propagation of inflammatory renal diseases, including lupus nephritis.

CD40 is a cell surface molecule expressed on a variety of cells and interacts with a 30-33 kDa activation-induced CD4+ T cell counterreceptor termed CD40L. CD40L-CD40 interactions have been extensively studied in T cell-B cell interactions and are essential for T cell dependent B cell differentiation and IgG, IgA and IgE production. CD40 is also expressed on monocytes, dendritic cells, epithelial cells, endothelial cells and fibroblasts. CD40 expression on these cells is upregulated in vitro by cytokines, most notably IFN-γ. In vivo studies have demonstrated markedly upregulated CD40 expression in inflammatory sites, such as rheumatoid arthritis synovial membrane or psoriatic plaques. In vitro studies utilizing anti-CD40 mAb or CD40L+ cells demonstrate that CD40 is functionally expressed on monocytes, dendritic cells, epithelial cells, endothelial cells and fibroblasts.

Earlier disclosure of treating idiopathic autoimmune diseases, including drug-induced lupus, such as International Patent Publication No. WO 93/09812 (published May 27, 1993) was based on the finding that CD40 is expressed on the surface of B cells. The initiation point of lupus is the deposition of autoantibodies in the kidney, which then attracts cells involved in destruction of kidney tissue. The finding, discussed below, that CD40 is expressed on kidney tubule cells provides the basis for treating inflammatory kidney diseases having initiation points other than autoantibody deposition.

Summary of the Invention

This invention provides a method of inhibiting activation by CD40 ligand of renal cells bearing CD40 on the surface of the cells, comprising contacting the cells with an agent capable of inhibiting interaction between CD40 ligand and CD40 on the cells, the agent being present in an amount effective to inhibit activation of the cells.

This invention provides a method of inhibiting activation by CD40 ligand of renal cells bearing CD40 on the surface of the cells, in a subject, comprising administering to the subject an agent capable of inhibiting interaction between CD40 ligand and CD40 on the cells, the agent being present in an amount effective to inhibit activation of the cells in the subject.

This invention provides a method of treating, in a subject, an inflammatory kidney disease, comprising administering to the subject an agent capable of inhibiting interaction between CD40 ligand and CD40 on the cells, the agent being present in an amount effective to inhibit activation of the cells in the subject and thereby treat the inflammatory kidney disease.

Description of the Figures

Figures 1A-Y: Atomic coordinates of crystal structure of soluble extracellular fragment of human CD40L containing residues Gly116-Leu261 (in Brookhaven Protein Data Bank format). (SEQ ID NO:1).

Figures 2A-C: Expression of CD40 in normal kidney. Shown are frozen sections of normal kidney stained with control mouse IgG (Figure 2A, magnification 25x) or anti-CD40 mAb G28.5 (Figures 2B and 2C, magnification 40x). Distal tubules and interstitial capillaries express CD40 while proximal tubules are $CD40^-$ (Figure 2B). Glomerular cells and epithelial cells of Bowmans capsule express CD40 (Figure 2C).

Figures 3A-C: Expression of CD40 in diffuse proliferative lupus nephritis. Shown are frozen sections of a kidney biopsy from a patient with Class IV lupus nephritis stained with control mouse IgG (Figure 3A, magnification 25x) or anti-CD40 mAb G28.5 (Figures 3B and 3C, magnification 40x). Figure 3B shows intense CD40 staining of distal and proximal tubules. Figure 3C shows increased and diffuse CD40 expression in the glomerulus. Figure 3C also shows that the epithelial derived crescent is CD40+.

Figure 4A: CD40L expression on interstitial mononuclear cells in class IV lupus glomerulonephritis. Shown is a frozen section obtained from a renal biopsy

specimen stained with anti-CD40L mAb 5c8. Bound antibody was visualized with the Vectastain ABC Elite kit followed by the chromogen 3-amino-9-ethylcarbazole (Vector Laboratories). The tissue was counterstained with Mayer's hematoxylin (Sigma). CD40L immunoreactivity is noted as staining of mononuclear cells.

Figure 4B: Isotype control staining of interstitial mononuclear cells in class IV lupus glomerulonephritis. Shown is a frozen section obtained from the same patient studied in Figure 4A and stained with an IgG2a isotype control mAb. Bound antibody was visualized with the Vectastain ABC Elite kit followed by the chromogen 3-amino-9-ethylcarbazole (Vector Laboratories). The tissue was counterstained with Mayer's hematoxylin (Sigma). Note the lack of immunoreactivity (staining).

Figure 5: CD40L expression on interstitial mononuclear cells in class IV lupus glomerulonephritis. Shown is a frozen section obtained from a renal biopsy specimen stained with anti-CD40L mAb 5c8. This specimen was obtained from a different patient than shown in Figure 4A. Bound antibody was visualized with the Vectastain ABC Elite kit followed by the chromogen 3-amino-9-ethylcarbazole (Vector Laboratories). The tissue was counterstained with Mayer's hematoxylin (Sigma). CD40L immunoreactivity is noted as staining of mononuclear cells.

Staining with an isotype control mAb was negative (not shown).

Figure 6: Renal CD40 expression in focal segmental glomerulosclerosis (FSGS). Shown is a frozen section obtained from a renal biopsy specimen stained with anti-CD40 mAb G28.5. Bound antibody was visualized with the Vectastain ABC Elite kit followed by the chromogen 3-amino-9-ethylcarbazole (Vector Laboratories). The tissue was counterstained with Mayer's hematoxylin (Sigma). Note the intense CD40 staining. Staining with an isotype control mAb was negative (not shown).

Figure 7: CD40L expression on interstitial mononuclear cells in focal segmental glomerulosclerosis. Shown is a frozen section obtained from the same patient as studied in Figure 6 stained with anti-CD40L mAb 5c8. Bound antibody was visualized with the Vectastain ABC Elite kit followed by the chromogen 3-amino-9-ethylcarbazole (Vector Laboratories). The tissue was counterstained with Mayer's hematoxylin (Sigma). CD40L immunoreactivity is noted as staining of mononuclear cells. Staining with an isotype control mAb was negative (not shown).

Figure 8: Renal CD40 expression in IgA nephropathy. Shown is a frozen section obtained from a renal biopsy specimen stained with anti-CD40 mAb G28.5. Bound antibody was visualized with the Vectastain ABC Elite

kit followed by the chromogen 3-amino-9-ethylcarbazole (Vector Laboratories). The tissue was counterstained with Mayer's hematoxylin (Sigma). Note the intense CD40 staining. Staining with an isotype control mAb was negative (not shown).

Figure 9: CD40L expression on interstitial mononuclear cells in IgA nephropathy. Shown is a frozen section obtained from the same patient as studied in Figure 8 stained with anti-CD40L mAb 5c8. Bound antibody was visualized with the Vectastain ABC Elite kit followed by the chromogen 3-amino-9-ethylcarbazole (Vector Laboratories). The tissue was counterstained with Mayer's hematoxylin (Sigma). CD40L immunoreactivity is noted as staining of mononuclear cells. Staining with as isotype control mAb was negative (not shown).

Detailed Description

This invention provides a method of inhibiting activation by CD40 ligand of renal cells bearing CD40 on the cell surface, comprising contacting the cells with an agent capable of inhibiting interaction between CD40 ligand and CD40 on the cells, the agent being present in an amount effective to inhibit activation of the cells. In one embodiment of this invention the agent is capable of inhibiting any interaction between CD40 ligand and CD40. "Interaction between CD40 ligand and CD40 on the cells" refers to one or more aspects, functional or structural, of a CD40-CD40 ligand interrelationship. Therefore, in one embodiment, an agent which inhibits interaction may competitively bind to CD40 ligand in such a way to block or diminish the binding of CD40 ligand to cellular CD40. In another embodiment an agent which inhibits interaction may associate with CD40 or CD40 ligand in a manner which does not inhibit binding of CD40 ligand to cellular CD40, but which influences the cellular response to the CD40 ligation, such as by altering the turnover rate of the cellular CD40 or the CD40-agent complex, by altering binding kinetics of CD40 with CD40 ligand, or by altering the rate or extent of cellular activation in response to CD40 ligation.

In specific embodiments the CD40-bearing renal cells are selected from the group consisting of glomerular endothelial cells, mesangial cells, distal tubule cells, proximal tubule cells, parietal epithelial cells, visceral epithelial cells, cells of a Henle loop or limb thereof, and interstitial inflammatory cells. In a more specific embodiment the parietal epithelial cells are crescent parietal epithelial cells.

In an embodiment of this invention the agent inhibits binding of CD40 ligand to CD40 on the cells.

In an embodiment of this invention the agent is a protein.

In another embodiment of this invention the agent is a nonprotein. As used herein the term nonprotein includes any and all compounds or agents which encompass elements other than simple or conjugated polypeptide chains. This includes elements such as amino acids having non-peptide linkages; nonprotein amino acids such as β, γ, or δ amino acids, amino acids in D configuration, or other nonprotein amino acids including homocysteine, homoserine, citrulline, ornithine, γ-aminobutyric acid, canavanine, djenkolic acid, or β-cyanoalanine; monosaccharides, polysaccharides, or carbohydrate moieties; fatty acids or lipid moieties; nucleotide moieties, mineral moieties; or other nonprotein elements.

In a specific embodiment the protein comprises an antibody or portion thereof capable of inhibiting interaction between CD40 ligand and CD40 on the cells. The antibody is a monoclonal or polyclonal antibody. In a more specific embodiment the monoclonal antibody specifically binds to the epitope to which monoclonal antibody 5c8 (ATCC Accession No. HB 10916) specifically binds. An example of such a monoclonal antibody is monoclonal antibody 5c8 (ATCC Accession No. HB 10916). In another embodiment, the antibody specifically binds to CD40. One example of an anti-CD40 antibody is the monoclonal mouse anti-human CD40, available from Genzyme Customer Service (Product 80-3702-01, Cambridge, MA). In other embodiments the monoclonal antibody is a chimeric antibody, a primatized antibody, a humanized antibody, or an antibody which includes a CDR region from a first human and an antibody scaffold from a second human.

The meaning of "chimeric", "primatized" and "humanized"

antibody and methods of producing them are well known to those of skill in the art. See, for example, PCT International Publication No. WO 90/07861, published July 26, 1990 (Queen, et al.); and Queen, et al. Proc. Nat'l Acad. Sci.-USA (1989) 86: 10029). Methods of making primatized antibodies are disclosed, for example, in PCT International publication No. WO/02108, corresponding to International Application No. PCT/US92/06194 (Idec Pharmaceuticals); and in Newman, et al., Biotechnology (1992) 10:1455-1460, which are hereby incorporated by reference into this application.

Generally, a humanized antibody is an antibody comprising one or more complementarity determining regions (CDRs) of a non-human antibody functionally joined to human framework region segments. Additional residues associated with the non-human antibody can optionally be present. Typically, at least one heavy chain or one light chain comprises non-human CDRs. Typically, the non-human CDRs are mouse CDRs. Generally, a primatized antibody is an antibody comprising one or more complementarity determining regions (CDRs) of an antibody of a species other than a non-human primate, functionally joined to framework region segments of a non-human primate. Additional residues associated with the species from which the CDR is derived can optionally be present. Typically, at least one heavy chain or one light chain comprises CDRs of the species which is not a nonhuman primate. Typically, the CDRs are human CDRs. Generally, a chimeric antibody is an antibody whose light and/or heavy chains contain regions from different species. For example one or more variable (V) region segments of one species may be joined to one or more constant (C) region segments of another species. Typically, a chimeric antibody contains variable region segments of a mouse joined to human constant region segments, although other mammalian species may be used.

Monoclonal antibody 5c8 is produced by a hybridoma cell which was deposited on November 14, 1991 with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. The hybridoma was accorded ATCC Accession Number HB 10916.

In a specific embodiment the portion of the antibody comprises a complementarity determining region or variable region of a light or heavy chain. In another specific embodiment the portion of the antibody comprises a complementarity determining region or a variable region. In another specific embodiment the portion of the antibody comprises a Fab or a single chain antibody. A single chain antibody is made up of variable regions linked by protein spacers in a single protein chain.

In another embodiment the protein comprises soluble extracellular region of CD40 ligand, or portion thereof, or variant thereof, capable of inhibiting any interaction between CD40 ligand and CD40 on the cells; or soluble extracellular region of CD40, or portion thereof, or variant thereof, capable of inhibiting any interaction between CD40 ligand and CD40 on the cells. In a specific embodiment the soluble extracellular region of CD40 ligand or CD40 is a monomer. In another embodiment the soluble extracellular region of CD40 is an oligomer.

Variants can differ from naturally occurring CD40 or CD40 ligand in amino acid sequence or in ways that do not involve sequence, or both. Variants in amino acid sequence are produced when one or more amino acids in naturally occurring CD40 or CD40 ligand is substituted with a different natural amino acid, an amino acid derivative or non-native amino acid. Particularly

preferred variants include naturally occurring CD40 or CD40 ligand, or biologically active fragments of naturally occurring CD40 or CD40 ligand, whose sequences differ from the wild type sequence by one or more conservative amino acid substitutions, which typically have minimal influence on the secondary structure and hydrophobic nature of the protein or peptide. Variants may also have sequences which differ by one or more non-conservative amino acid substitutions, deletions or insertions which do not abolish the CD40 or CD40 ligand biological activity. Conservative substitutions typically include the substitution of one amino acid for another with similar characteristics such as substitutions within the following groups: valine, glycine; glycine, alanine; valine, isoleucine; aspartic acid,glutamic acid; asparagine,glutamine; serine,threonine;lysine, arginine; and phenylalanine,tyrosine. The non-polar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine and glutamine. The positively charged (basic) amino acids include arginine, lysine and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

Other conservative substitutions can be taken from Table 1, and yet others are described by Dayhoff in the Atlas of Protein Sequence and Structure (1988).

Table 1: Conservative Amino Acid Replacements

For Amino Acid	Code	Replace with any of
Alanine	A	D-Ala, Gly,beta-ALa, L-Cys,D-Cys
Arginine	R	D-Arg, Lys,homo-Arg, D-homo-Arg, Met,D-Met, Ile, D-Ile, Orn, D-Orn
Asparagine	N	D-Asn,Asp,D-Asp,Glu,D-Glu, Gln,D-Gln
Aspartic Acid	D	D-Asp,D-Asn,Asn, Glu,D-Glu, Gln, D-Gln
Cysteine	C	D-Cys, S-Me-Cys,Met,D-Met,Thr, D-Thr
Glutamine	Q	D-Gln,Asn, D-Asn,Glu,D-Glu,Asp, D-Asp
Glutamic Acid	E	D-Glu,D-Asp,Asp, Asn, D-Asn, Gln, D-Gln
Glycine	G	Ala, D-Ala,Pro, D-Pro, Beta-Ala, Acp
Isoleucine	I	D-Ile, Val, D-Val, Leu, D-Leu, Met, D-Met
Leucine	L	D-Leu, Val, D-Val, Met, D-Met
Lysine	K	D-Lys,Arg, D-Arg, homo-Arg, D-homo-Arg, Met, D-Met, Ile, D-Ile, Orn, D-Orn
Methionine	M	D-Met, S-Me-Cys, Ile, D-Ile, Leu, D-Leu, Val, D-Val, Norleu
Phenylalanine	F	D-Phe,Tyr, D-Thr,L-Dopa,His,D-His, Trp, D-Trp, Trans 3,4 or 5-phenylproline, cis 3,4 or 5 phenylproline
Proline	P	D-Pro, L-I-thioazolidine-4-carboxylic acid, D- or L-1-oxazolidine-4-carboxylic acid

Serine	S	D-Ser, Thr, D-Thr, allo-Thr, Met, D-Met, Met(O), D-Met(O), Val, D-Val
Threonine	T	D-Thr, Ser, D-Ser, allo-Thr, Met, D-Met, Met(O) D-Met(O), Val, D-Val
Tyrosine	Y	D-Tyr,Phe, D-Phe, L-Dopa, His,D-His
Valine	V	D-Val, Leu,D-Leu,Ile,D-Ile, Met, D-Met

Other variants within the invention are those with modifications which increase peptide stability. Such variants may contain, for example, one or more non-peptide bonds (which replace the peptide bonds) in the peptide sequence. Also included are: variants that include residues other than naturally occurring L-amino acids, such as D-amino acids or non-naturally occurring or synthetic amino acids such as beta or gamma amino acids and cyclic variants. Incorporation of D- instead of L-amino acids into the polypeptide may increase its resistance to proteases. See, e.g., U.S. Patent 5,219,990.

The peptides of this invention may also be modified by various changes such as insertions, deletions and substitutions, either conservative or nonconservative where such changes might provide for certain advantages in their use.

In other embodiments, variants with amino acid substitutions which are less conservative may also result in desired derivatives, e.g., by causing changes in charge, conformation and other biological properties. Such substitutions would include for example, substitution of hydrophilic residue for a hydrophobic

residue, substitution of a cysteine or proline for another residue, substitution of a residue having a small side chain for a residue having a bulky side chain or substitution of a residue having a net positive charge for a residue having a net negative charge. When the result of a given substitution cannot be predicted with certainty, the derivatives may be readily assayed according to the methods disclosed herein to determine the presence or absence of the desired characteristics.

Variants within the scope of the invention include proteins and peptides with amino acid sequences having at least eighty percent homology with the extracellular region of CD40 or the extracellular region of CD40 ligand. More preferably the sequence homology is at least ninety percent, or at least ninety-five percent.

Just as it is possible to replace substituents of the scaffold, it is also possible to substitute functional groups which decorate the scaffold with groups characterized by similar features. These substitutions will initially be conservative, i.e., the replacement group will have approximately the same size, shape, hydrophobicity and charge as the original group. Non-sequence modifications may include, for example, in vivo or in vitro chemical derivatization of portions of naturally occurring CD40 or CD40 ligand, as well as changes in acetylation, methylation, phosphorylation, carboxylation or glycolsylation.

In a further embodiment the protein, including the extracellular region of CD40 ligand and CD40, is modified by chemical modifications in which activity is preserved. For example, the proteins may be amidated, sulfated, singly or multiply halogenated, alkylated, carboxylated, or phosphorylated. The protein may also be singly or multiply acylated, such as with an acetyl group, with a

farnesyl moiety, or with a fatty acid, which may be saturated, monounsaturated or polyunsaturated. The fatty acid may also be singly or multiply fluorinated. The invention also includes methionine analogs of the protein, for example the methionine sulfone and methionine sulfoxide analogs. The invention also includes salts of the proteins, such as ammonium salts, including alkyl or aryl ammonium salts, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogen phosphate, thiosulfate, carbonate, bicarbonate, benzoate, sulfonate, thiosulfonate, mesylate, ethyl sulfonate and benzensulfonate salts.

The soluble, monomeric CD40-L protein can comprise all or part of the extracellular region of CD40-L. The extracellular region of CD40-L contains the domain that binds to CD40. Thus, soluble CD40-L can inhibit the interaction between CD40L and the CD40-bearing cell. This invention contemplates that sCD40-L may constitute the entire extracellular region of CD40-L, or a fragment or derivative containing the domain that binds to CD40.

Soluble CD40 protein (sCD40) comprises the extracellular region of CD40. sCD40 inhibits the interaction between CD40L and CD40-bearing cells. sCD40 may be in monomeric or oligomeric form.

In another embodiment of this invention the protein comprising soluble extracellular region of CD40 or portion thereof further comprises an Fc region fused to the extracellular region of CD40 or portion thereof. In a specific embodiment the Fc region is capable of binding to protein A or protein G. In another embodiment the Fc region comprises IgG, IgG_1, IgG_2, IgG_3, IgG_4, IgA, IgA_1, IgA_2, IgM, IgD, or IgE.

The soluble CD40/Fc fusion protein can be prepared using

conventional techniques of enzymes cutting and ligation of fragments from desired sequences. Suitable Fc regions for the fusion protein are Fc regions that can bind to protein A or protein G, or that are capable of recognition by an antibody that can be used in purification or detection of a fusion protein comprising the Fc region. For example, the Fc region may include the Fc region of human IgG_1 or murine IgG_1. This invention also provides a nucleic acid molecule which encodes the CD40/Fc fusion protein.

The method of creating soluble forms of membrane molecules by recombinant means, in which sequences encoding the transmembrane and cytoplasmic domains are deleted, is well known. See generally Hammonds et al., U.S. Patent No. 5,057,417. In addition, methods of preparing sCD40 and CD40/Fc fusion protein are well-known. See, e.g., PCT International Publication No. WO 93/08207; Fanslow et al., "Soluble Forms of CD40 Inhibit Biologic Responses of Human B Cells, "J. Immunol., vol. 149, pp.655-60 (July 1992).

In an embodiment of this invention, the agent is selected by a screening method.

In a specific embodiment the agent is selected by a screening method, which comprises isolating a sample of cells; culturing the sample under conditions permitting activation of CD40-bearing cells; contacting the sample with cells expressing a protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession no. HB 10916, or with a protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession no. HB 10916, effective to activate the CD40-bearing cells; contacting the sample with an amount of the agent effective to inhibit activation of the CD40-

bearing cells if the agent is capable of inhibiting activation of the CD40-bearing cells; and determining whether the cells expressing the protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession no. HB 10916, or with the protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession no. HB 10916, activate the CD40-bearing cells in the presence of the agent. The cell sample may be isolated from diverse tissues, including cell lines in culture or cells isolated from an animal, such as dispersed cells from a solid tissue, cells derived from a bone marrow biopsy, or cells isolated from a body fluid such as blood or lymphatic fluid.

In another specific embodiment the agent (molecule) is selected based on a three-dimensional structure of soluble extracellular region of CD40 ligand or portion thereof capable of inhibiting interaction between CD40 ligand and CD40 on the cells. The agent may be selected from a library of known agents, modified from a known agent based on the three-dimensional structure, or designed and synthesized de novo based on the three-dimensional structure. In specific embodiments the agent (molecule) is designed by structure optimization of a lead inhibitory agent based on a three-dimensional structure of a complex of the soluble extracellular region of CD40 ligand or portion thereof with the lead inhibitory agent. A lead inhibitory agent is a molecule which has been identified which, when it is contacted with CD40 ligand, binds to and complexes with the soluble extracellular region of CD40 ligand, CD40, or portion thereof, thereby decreasing the ability of the complexed or bound CD40 ligand or CD40 ligand portion to activate CD40-bearing cells. In another embodiment, a lead inhibitory agent may act by interacting with either the

extracellular region of CD40 ligand, CD40, or in a tertiary complex with both a portion of CD40 ligand and CD40, decreasing the ability of the complexed CD40 ligand-CD40 to activate the CD40-bearing cells. In the methods of the invention, the CD40 ligand may be either soluble or bound to cells such as activated T cells, and may be either full length native CD40 ligand or portions thereof. Decreased ability to activate CD40-bearing cells may be measured in different ways. One way it may be measured is by showing that CD40 ligand, in the presence of inhibitor, causes a lesser degree of activation of CD40-bearing cells, as compared to treatment of the cells with a similar amount of CD40 ligand without inhibitor under similar conditions. Decreased ability to activate CD40-bearing cells may also be indicated by a higher concentration of inhibitor-CD40 ligand complex being required to produce a similar degree of activation of CD40-bearing cells under similar conditions, as compared to unbound CD40 ligand. At the extreme, the inhibitor-contacted CD40 ligand may be unable to activate CD40-bearing cells at concentrations and under conditions which allow activation of these cells by unbound CD40 ligand or a given portion thereof.

The agent (molecule) can be selected by a computational screening method using the crystal structure of a soluble fragment of the extracellular domain of human CD40L containing residues Gly116-Leu261 (sCD40L(116-261)).

The crystal structure to be used with the screening method has been determined at 2 Å resolution by the method of molecular replacement. In brief, a soluble fragment of the extracellular domain of human CD40 ligand containing amino acid residues Gly 116 to the c-terminal residue Leu 261 was first produced in soluble form, then purified and crystallized. The crystals were used to collect diffraction data. Molecular replacement and

refinement were done with the XPLOR program package and QUANTA (Molecular Simulations, Inc.) Software. In particular, a 3-dimensional model of human sCD40L was constructed using the murine CD40L model using QUANTA protein homology modeling software. This model was used as a probe for crystallographic analysis calculations and refined using XPLOR. This method of determining the crystal structure of sCD40L is described in more detail in Karpusas et al., "2 Å crystal structure of an extracellular fragment of human CD40 ligand," Structure (October 1995) 3(10):1031-1039. The atomic coordinates of sCD40L(116-261) are provided in Figures 1A-Y. The screening method for selecting an agent includes computational drug design and iterative structure optimization, as described below.

The agent may be an inhibitor selected using computational drug design. Using this method, the sCD40L crystal structure coordinates are used as an input for a computer program, such as DOCK, which outputs a list of molecular structures that are expected to bind to CD40L. Use of such computer programs is well-known. See, e.g., Kuntz, "Structure-Based Strategies for drug design and discovery," Science, vol. 257, p. 1078 (1992). The list of molecular structures can then be screened by biochemical assays for CD40L binding. Competition-type biochemical assays, which are well known, can be used. See, e.g., Bajorath et al., "Identification of residues of CD40 and its ligand which are critical for the receptor-ligand interaction," Biochemistry, 34, p. 1833 (1995). The structures that are found to bind to CD40L can thus be used as agents for the present invention. The agent may also be a modified or designed molecule, determined by interactive cycles of structure optimization. Using this approach, a small molecule inhibitor of CD40L found using the above computational approach or other approach can be co-crystallized with sCD40L and the crystal

structure of the complex solved by molecular replacement. The information revealed through molecular replacement can be used to optimize the structure of the inhibitors by clarifying how the molecules interact with CD40L. The molecule may be modified to improve its physiochemical properties, including specificity and affinity for CD40L.

In an embodiment of this invention the agent is a small molecule. As used herein a small molecule is a compound having a molecular weight between 20 Da and $1x10^6$ Da, preferably from 50 Da to 2 kDa.

This invention also provides a method of inhibiting activation by CD40 ligand of renal cells bearing CD40 on the surface of the cells, in a subject, comprising administering to the subject an agent capable of inhibiting interaction between CD40 ligand and CD40 on the cells, the agent being present in an amount effective to inhibit activation of the cells in the subject.

In specific embodiments the CD40-bearing renal cells are selected from the group consisting of glomerular endothelial cells, mesangial cells, distal tubules, proximal tubules, parietal epithelial cells, visceral epithelial cells, cells of a Henle loop or limb thereof, and interstitial inflammatory cells. In a more specific embodiment the parietal epithelial cells are crescent parietal epithelial cells.

In an embodiment of this invention the agent inhibits binding of CD40 ligand to CD40 on the cells.

In an embodiment of this invention the agent is a protein. In another embodiment of this invention the agent is a nonprotein.

In a specific embodiment the protein comprises an

antibody or portion thereof capable of inhibiting any interaction between CD40 ligand and CD40 on the cells. The antibody is a monoclonal or polyclonal antibody. In a more specific embodiment the monoclonal antibody specifically binds to the epitope to which monoclonal antibody 5c8 (ATCC Accession No. HB 10916) specifically binds. An example of such a monoclonal antibody is monoclonal antibody 5c8 (ATCC Accession No. HB 10916). In other embodiments the monoclonal antibody is a chimeric antibody or a humanized antibody.

In a specific embodiment the portion of the antibody comprises a complementarity determining region or variable region of a light or heavy chain. In another specific embodiment the portion of the antibody comprises a complementarity determining region or a variable region. In another specific embodiment the portion of the antibody comprises a Fab or a single chain antibody.

In another embodiment the protein comprises soluble extracellular region of CD40 ligand or portion thereof capable of inhibiting any interaction between CD40 ligand and CD40 on the cells; or soluble extracellular region of CD40 or portion thereof capable of inhibiting any interaction between CD40 ligand and CD40 on the cells. In a specific embodiment the soluble extracellular region of CD40 ligand or CD40 is a monomer. In another embodiment the soluble extracellular region of CD40 is an oligomer.

In another embodiment of this invention the protein comprising soluble extracellular region of CD40 or portion thereof further comprises an Fc region fused to the extracellular region of CD40 or portion thereof. In a specific embodiment the Fc region is capable of binding to protein A or protein G. In another specific embodiment the Fc region comprises IgG, IgG_1, IgG_2, IgG_3,

IgG_4, IgA, IgA_1, IgA_2, IgM, IgD, or IgE.

The subject which can be treated by the above-described methods is an animal. Preferably the animal is a mammal. Examples of mammals which may be treated include, but are not limited to, humans, non-human primates, rodents (including rats, mice, hamsters and guinea pigs) cow, horse, sheep, goat, pig, dog and cat.

In an embodiment of this invention, the agent is selected by a screening method.

In a specific embodiment the agent is selected by a screening method, which comprises isolating a sample of cells; culturing the sample under conditions permitting activation of CD40-bearing cells; contacting the sample with cells expressing a protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession no. HB 10916, or with a protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession no. HB 10916, effective to activate the CD40-bearing cells; contacting the sample with an amount of the agent effective to inhibit activation of the CD40-bearing cells if the agent is capable of inhibiting activation of the CD40-bearing cells; and determining whether the cells expressing the protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession no. HB 10916, or with the protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession no. HB 10916, activate the CD40-bearing cells in the presence of the agent. The cell sample may be isolated from diverse tissues, including cell lines in culture or cells isolated from an animal, such as dispersed cells from a solid tissue, cells derived from a bone marrow biopsy, or cells

isolated from a body fluid such as blood or lymphatic fluid.

In another specific embodiment the molecule (agent) is selected based on a three-dimensional structure of soluble extracellular region of CD40 ligand or portion thereof capable of inhibiting any interaction between CD40 ligand and CD40 on the cells. The molecule may be selected from a library of known molecules, modified from a known molecule based on the three-dimensional structure, or designed and synthesized de novo based on the three-dimensional structure. In specific embodiments the agent or molecule is designed by structure optimization of a lead inhibitory agent based on a three-dimensional structure of a complex of the soluble extracellular region of CD40 ligand or portion thereof with the lead inhibitory agent.

Method of Treatment

This invention provides a method of treating, in a subject, an inflammatory kidney disease, comprising the above-described method of inhibiting activation by CD40 ligand of renal cells bearing CD40 on the surface of the cells, which comprises administering to the subject an agent capable of inhibiting interaction between CD40 ligand and CD40 on the cells, the agent being present in an amount effective to inhibit activation of the cells in the subject, thereby treating the inflammatory kidney disease.

The inflammatory kidney disease may be one which is initiated by autoantibody deposition in kidney, or one which is not initiated by autoantibody deposition in kidney. Many kidney diseases for which the methods of the invention are useful include ones which have multifactorial etiology.

In an embodiment of this invention the kidney disease is selected from the group consisting of: membranous glomerulonephritis, minimal change disease/acute tubular necrosis; pauci-immune glomerulonephritis; focal segmental glomerulosclerosis; interstitial nephritis; antitissue antibody-induced glomerular injury, such as anti-basement membrane antibody disease; circulating immune-complex disease; glomerulopathies associated with multisystem diseases; drug-induced glomerular disease; renal transplant rejection; rapidly progressive glomerulonephritis; and post-streptococcal glomerulonephritis. Circulating immune-complex diseases include infective endocarditis, leprosy, syphilis, hepatitis B, malaria, and diseases of endogenous antigens such as DNA, thyroglobulin, autologous immunoglobulins, erythrocyte stroma, renal tubule antigens, and tumor-specific or tumor-associated antigens. Glomerulopathies associated with multisystem diseases include diabetic nephropathy, systemic lupus erythematosus, Goodpasture's disease, vasculitis, multiple myeloma, Waldenström's macroglobulinemia, and amyloidosis. In specific embodiments the vasculitis is Henoch-Schönlein purpura, polyarteritis nodosa (sometimes called polyarteritis), Wegener's granulomatosis, cryoglobulinemia (sometimes called cryoimmunoglobulinemia). The kidney disease may also be one which affects the renal tubules, such as toxins, neoplasias, hypersensitivity nephropathy, Sjögren's syndrome, and AIDS. In a specific embodiment the pauci-immune glomerulonephritis is ANCA+ pauci-immune glomerulonephritis, or Wegener's granulomatosis. In another specific embodiment the interstitial nephritis is drug-induced interstitial nephritis.

The compounds of this invention may be administered in any manner which is medically acceptable. This may include injections, by parenteral routes such as intravenous, intravascular, intraarterial, subcutaneous,

intramuscular, intratumor, intraperitoneal, intraventricular, intraepidural, or others as well as oral, nasal, ophthalmic, rectal, topical, or inhaled. Sustained release administration is also specifically included in the invention, by such means as depot injections of erodible implants directly applied during surgery.

The compounds are administered at any dose per body weight and any dosage frequency which is medically acceptable. Acceptable dosage includes a range of between about 0.01 and 200 mg/kg subject body weight. A preferred dosage range is between about 0.1 and 50 mg/kg. Particularly preferred is a dose of between about 1 and 30 mg/kg. The dosage is repeated at intervals ranging from each day to every other month. One preferred dosing regimen is to administer a compound of the invention daily for the first three days of treatment, after which the compound is administered every 3 weeks, with each administration being intravenously at 5 or 10 mg/kg body weight. Another preferred regime is to administer a compound of the invention daily intravenously at 5 mg/kg body weight for the first three days of treatment, after which the compound is administered subcutaneously or intramuscularly every week at 10 mg per subject. Another preferred regime is to administer a single dose of the compound of the invention parenterally at 20 mg/kg body weight, followed by administration of the compound subcutaneously or intramuscularly every week at 10 mg per subject.

The compounds of the invention may be administered as a single dosage for certain indications such as preventing immune response to an antigen to which a subject is exposed for a brief time, such as an exogenous antigen administered on a single day of treatment. Examples of such an antigen would include coadministration of a

compound of the invention along with a gene therapy vector, or a therapeutic agent such as an antigenic pharmaceutical or a blood product. In indications where antigen is chronically present, such as in controlling immune reaction to transplanted tissue or to chronically administered antigenic pharmaceuticals, the compounds of the invention are administered at intervals for as long a time as medically indicated, ranging from days or weeks to the life of the subject.

Inflammatory responses are characterized by redness, swelling, heat and pain, as consequences of capillary dilation with edema and migration of phagocytic leukocytes. Inflammation is further defined by Gallin (Chapter 26, Fundamental Immunology, 2d Ed., Raven Press, New York, 1989, pp. 721-733), which is herein incorporated by reference.

This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

Experimental Details

CD40 expression in normal kidney and in renal biopsy specimens obtained from patients with systemic lupus erythematosus and other kidney diseases was examined.

Patients and Methods

Immunohistochemistry

Immunohistochemical analyses of frozen sections were performed with a Vectastain Elite Kit (Vector,

Burlingame, CA) as previously described. Briefly, the tissue was first blocked with PBS containing horse serum and 1% BSA and additional blocking was obtained utilizing an Avidin/Biotin Blocking Kit also purchased from Vector. The sections were then stained with 1:1000 dilutions of anti-CD40 mAb G28.5 or an isotype control mAb in PBS followed by biotinylated horse anti-mouse IgG. Endogenous peroxidase activity was blocked with 1:400 dilution of H_2O_2. Bound antibody was visualized with the Vectastain ABC reagent followed by the chromogen 3-amino-9-ethylcarbazole (Vector Laboratories). The tissue was counterstained with Mayer's hematoxylin (Sigma).

Staining was evaluated visually. In the following tables "0" indicates no staining; 1+ indicates minimal staining; 2+ indicates moderate staining; and 3+ indicates intense staining.

Results

Analysis of CD40 expression in normal kidney

Initial studies of renal CD40 expression were prompted by the observation that CD40 is normally expressed on endothelial cells in a variety of tissues. Consistent with this finding, it was found that renal interstitial capillaries and larger vessels express CD40. CD40 was also found to be expressed on other renal parenchymal cells, such as glomerular endothelial cells, glomerular mesangial cells and parietal epithelial cells of Bowman's capsule. Glomerular visceral epithelial cells do not express CD40. Distal tubules are strongly immunoreactive for CD40 and staining was most intense along the basolateral membrane. In contrast, proximal tubules are not immunoreactive with anti-CD40 mAb. An isotype control mAb did not stain renal specimens. The immunoreactivity noted with anti-CD40 mAb G28.5 is most

likely specific and does not represent cross-reactivity because similar staining was noted with an additional anti-CD40 mAb. Thus it is concluded that renal parenchymal cells differentially express CD40.

Analysis of renal CD40 expression in systemic lupus erythematosus

Whether renal CD40 expression is upregulated in lupus glomerulonephritis was analyzed. Frozen sections obtained from patient biopsy specimens were stained with anti-CD40 mAb G28.5 or an isotype control mAb.

Renal CD40 expression in systemic lupus erythematosus was analyzed. Patients with Class III and IV lupus nephritis tended to have increased CD40 expression on glomerular endothelial cells, mesangial cells and distal tubules. In addition, proximal tubules are CD40+ in patients with Class III and IV lupus nephritis. Also, there is striking CD40 expression on parietal epithelial cells in patients with crescent formation. CD40 is also present on interstitial inflammatory cells. The distribution and intensity of renal CD40 expression in patients with pure Class V disease was similar to that seen in normal kidney.

Whether renal CD40 upregulation was unique to systemic lupus erythematosus was investigated. To do so, CD40 expression was investigated in patients with the following renal diseases: membranous glomerulonephritis, minimal change disease/acute tubular necrosis, ANCA+ pauci-immune glomerulonephritis, focal segmental glomerulosclerosis and IgA nephropathy. Proximal tubule CD40 expression was upregulated in ANCA+ pauci-immune glomerulonephritis, focal segmental glomerulosclerosis and IgA nephropathy. In contrast, there was little

proximal tubule CD40 immunoreactivity in membranous glomerulonephritis or minimal change disease/acute tubular necrosis. Crescent parietal epithelial cells in IgA nephropathy are also striking CD40+. Interstitial inflammatory cells, when present, also express CD40. These findings demonstrate that CD40 expression is upregulated in a variety of inflammatory renal diseases. Moreover, these studies indicate that CD40L mediated interactions with renal parenchymal cells play roles in normal renal physiology and augment inflammatory responses in renal diseases.

Table 2: CD40 Expression In Normal Kidney

	Glomerular				Interstitium		Tubules		
Specimen	EC	Mesangial	VEC	PEC	Cap EC	Leukocytes	Proximal	Distal	Collecting
1	1+diffuse	1+	-	+/-	2+diffuse	-	-	2+diffuse	2+
2	1+	2+diffuse	-	1+focal	2+diffuse	1+(rare)	-	3+diffuse	3+
3									

Table 3: CD40 Expression In SLE Glomerulonephritis

		Interstitium		Tubules	
Patient	WHO Class	Cap EC	Leukocytes	Proximal	Distal
KC95-94	IIb	2+	0	-	2+
KC95-277	III	1+	3+	2+	3+
KC95-286	III/V	1+	1+	1+	2+
KC94-78	III-IV/V	1+	3+	2-3+	3+
KC95-308	IV	1+	1+	1+	2+
KC94-269	IV	1+	2+	2+	3+
K94-165	IV	1+	2+	2-3+	3+
K94-59	IV	1+	3+	3+	3+
K95-089	IV	1+	3+	2+	3+
K94-6	IV	2+	2+	3+	3+
K94-12	IV	3+	3+	1+	3+
K95-090	IV/V	2+	3+	1-2+	3+
K95-003	IV/V	2+	1+	2+	3+
KC95-264	IV/V	2+	3+	3+	3+
K95-7	V	2+	1+	0	2+
KC95-195	V	±	1	±	2
K94-142	V	1+	No leuk	-	2+
K95-12	V	1+	1+	1+	1+

Table 4: CD40 Expression In SLE Glomerulonephritis

Glomerular Expression

Patient	WHO Class	EC	Mesangial	VEC	PEC
KC95-277	III	0	1+	0	±
KC94-78	III-IV/V	3+	3+	0	1+
KC95-308	IV	2+	2+	0	1+
KC94-269	IV	3+	3+	0	1+
K94-165	IV	1+	2-3+	0	1+
K94-59	IV	3+	3+	0	3+
K95-089	IV	3+	2+	0	3+
K94-12	IV	3+	3+	0	±
K95-090	IV/V	1+	0	0	sclero
K95-003	IV/V	2+	1+	0	1+
KC95-264	IV/V	3+	3+	0	3+ (cresc)
K95-7	V	1+	1+	0	0
KC95-195	V	1	±	0	±
K94-142	V	0	1	0	-(par 1+)
K95-12	V	0	1	0	0(par 1+)

Table 5: CD40 Expression In Non-SLE Glomerulonephritis

		Glomerular Expression			
Patient	Renal Disease	EC	Mesangial	VEC	PEC
KC95-310	Membranous	0	1+	0	1+
KC95-299	MC/ATN	0	±	0	1+
KC95-312	Pauci-immune	1	1	0	
KC95-280	FSGS	0	±	0	
KC94-282	IgA	1+	2+	0	2+

Table 6: CD40 Expression In Non-SLE Glomerulonephritis

		Interstitium		Tubules	
Patient	Renal Disease	Cap EC	Leukocytes	Proximal	Distal
KC95-310	Membranous	1+	±	1+	2+
KC95-299	MC/ATN	±	2+	0	1+
KC95-312	Pauci-immune	1+	3+	2+	3+
KC95-280	FSGS	1+	3+	2+	3+
KC94-282	IgA	1+	3+	2+	3+

Analysis of renal CD40-ligand expression in inflammatory renal diseases

In situ CD40L expression was studied in renal biopsy specimens from patients with SLE GN (n=18), as well as in normal kidney and biopsy specimens from patients with IgA nephropathy, focal segmental glomerulosclerosis, minimal change disease, idiopathic membranous GN and ANCA$^+$ pauci-immune GN. Immunohistochemical studies were performed on frozen sections utilizing anti-CD40L mAb 5C8 or controls mAbs. Upregulation of CD40L expression is observed in class IV lupus glomerulonephritis **(Figures 4A, 4B and 5)**, focal segmental glomerulosclerosis **(Figure 7)** and Iga nephropathy **(Figure 9)**. CD40L expression is noted as dim, discrete staining of some infiltrating mononuclear cells. These results provide further evidence that CD40L mediated signals play a role in the immunopathogenesis of inflammatory glomerular or tubulointerstitial diseases by interacting with CD40$^+$ target cells in the kidney.

SEQUENCE LISTING

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(ii) TITLE OF INVENTION: THERAPEUTIC APPLICATIONS OF T-BAM (CD40-L) TECHNOLOGY TO TREAT INFLAMMATORY KIDNEY DISEASES

(iii) NUMBER OF SEQUENCES: 1

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 146 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Gly Asp Gln Asn Pro Gln Ile Ala Ala His Val Ile Ser Glu Ala Ser
1 5 10 15

Ser Lys Thr Thr Ser Val Leu Gln Trp Ala Glu Lys Gly Tyr Tyr Thr
20 25 30

Met Ser Asn Asn Leu Val Thr Leu Glu Asn Gly Lys Gln Leu Thr Val
35 40 45

Lys Arg Gln Gly Leu Tyr Tyr Ile Tyr Ala Gln Val Thr Phe Cys Ser
50 55 60

Asn Arg Glu Ala Ser Ser Gln Ala Pro Phe Ile Ala Ser Leu Cys Leu
65 70 75 80

Lys Ser Pro Gly Arg Phe Glu Arg Ile Leu Leu Arg Ala Ala Asn Thr
85 90 95

His Ser Ser Ala Lys Pro Cys Gly Gln Gln Ser Ile His Leu Gly Gly
100 105 110

Val Phe Glu Leu Gln Pro Gly Ala Ser Val Phe Val Asn Val Thr Asp
115 120 125

Pro Ser Gln Val Ser His Gly Thr Gly Phe Thr Ser Phe Gly Leu Leu
130 135 140

Lys Leu
145

What is claimed is:

1. A method of inhibiting activation by CD40 ligand of renal cells bearing CD40 on the surface of the cells, comprising contacting the cells with an agent capable of inhibiting interaction between CD40 ligand and CD40 on the cells, the agent being present in an amount effective to inhibit activation of the cells.

2. The method of claim 1, wherein the CD40-bearing renal cells are selected from the group consisting of glomerular endothelial cells, mesangial cells, distal tubule cells, proximal tubule cells, parietal epithelial cells, visceral epithelial cells, cells of a Henle limb, and interstitial inflammatory cells.

3. The method of claim 2, wherein the parietal epithelial cells are crescent parietal epithelial cells.

4. The method of claim 1, wherein the agent inhibits binding of CD40 ligand to CD40 on the cells.

5. The method of claim 1, wherein the agent is a protein.

6. The method of claim 5, wherein the protein comprises an antibody or portion thereof.

7. The method of claim 6, wherein the antibody is a monoclonal antibody.

8. The method of claim 7, wherein the monoclonal antibody specifically binds to the epitope to which monoclonal antibody 5c8 (ATCC Accession No. HB

10916) specifically binds.

9. The method of claim 8, wherein the monoclonal antibody is monoclonal antibody 5c8 (ATCC Accession No. HB 10916).

10. The method of claim 7, wherein the monoclonal antibody specifically binds to CD40.

11. The method of claim 10, wherein the antibody is humanized, chimeric, or primatized.

12. The method of claim 7, wherein the monoclonal antibody is a chimeric antibody.

13. The method of claim 7, wherein the monoclonal antibody is a humanized antibody.

14. The method of claim 6, wherein the portion of the antibody comprises a complementarity determining region or variable region of a light or heavy chain.

15. The method of claim 6, wherein the portion of the antibody comprises a complementarity determining region or a variable region.

16. The method of claim 15, wherein the portion of the antibody comprises a Fab or a single chain antibody.

17. The method of claim 5, wherein the protein comprises soluble extracellular region of CD40 ligand, or variant thereof including conservative substituents, or portion thereof; or soluble extracellular region of CD40, or variant thereof including conservative substituents, or portion thereof.

18. The method of claim 17, wherein the soluble

extracellular region of CD40 ligand or CD40 is a monomer.

19. The method of claim 17, wherein the soluble extracellular region of CD40 is an oligomer.

20. The method of claim 17, wherein the protein comprising soluble extracellular region of CD40 or portion thereof or CD40 ligand or portion thereof further comprises an Fc region fused to the extracellular region of CD40 or portion thereof or CD40 ligand or portion thereof.

21. The method of claim 20, wherein the Fc region is capable of binding to protein A or protein G.

22. The method of claim 21, wherein the Fc region comprises IgG, IgA, IgM, IgD, or IgE, or subclasses thereof.

23. The method of claim 22, wherein:
the IgG is IgG_1, IgG_2, IgG_3, or IgG_4; or
the IgA is IgA_1 or IgA_2.

24. The method of claim 1, wherein the agent is nonprotein.

25. The method of claim 1, wherein the agent is selected from a library of known agents.

26. The method of claim 1, wherein the agent is modified from a known agent.

27. The method of claim 26, wherein the modified agent is designed by structure optimization of a lead inhibitory agent based on a three-dimensional structure of a complex of soluble extracellular

region of CD40 ligand or portion thereof with the lead inhibitory agent.

28. The method of claim 1, wherein the agent is selected by a screening method, which comprises:

isolating a sample of cells;

culturing the sample under conditions permitting activation of CD40-bearing cells;

contacting the sample with cells expressing a protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession No. HB 10916, or with a protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession No. HB 10916, effective to activate the CD40-bearing cells;

contacting the sample with an amount of the agent effective to inhibit activation of the CD40-bearing cells if the agent is capable of inhibiting activation of the CD40-bearing cells; and

determining whether the cells expressing the protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession No. HB 10916, or with the protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession No. HB 10916, activate the CD40-bearing cells in the presence of the agent.

29. The method of claim 28, wherein the agent is

selected from a library of known agents.

30. The method of claim 29, wherein the known agents are nonprotein agents.

31. A method of inhibiting activation by CD40 ligand of renal cells bearing CD40 on the surface of the cells, in a subject, comprising administering to the subject an agent capable of inhibiting interaction between CD40 ligand and CD40 on the cells, the agent being present in an amount effective to inhibit activation of the cells in the subject.

32. The method of claim 31, wherein the CD40-bearing renal cells are selected from the group consisting of glomerular endothelial cells, mesangial cells, distal tubule cells, proximal tubule cells, parietal epithelial cells, visceral epithelial cells, cells of a Henle limb, and interstitial inflammatory cells.

33. The method of claim 32, wherein the parietal epithelial cells are crescent parietal epithelial cells.

34. The method of claim 31, wherein the agent inhibits binding of CD40 ligand to CD40 on the cells.

35. The method of claim 31, wherein the agent is a protein.

36. The method of claim 35, wherein the protein comprises an antibody or portion thereof.

37. The method of claim 36, wherein the antibody is a monoclonal antibody.

38. The method of claim 37, wherein the monoclonal antibody specifically binds to the epitope to which monoclonal antibody 5c8 (ATCC Accession No. HB 10916) specifically binds.

39. The method of claim 38, wherein the agent is monoclonal antibody 5c8 (ATCC Accession No. HB 10916).

40. The method of claim 37, wherein the monoclonal antibody specifically binds to CD40.

41. The method of claim 40, wherein the antibody is humanized, chimeric, or primatized.

42. The method of claim 37, wherein the monoclonal antibody is a chimeric antibody.

43. The method of claim 37, wherein the monoclonal antibody is a humanized antibody.

44. The method of claim 36, wherein the portion of the antibody comprises a complementarity determining region or variable region of a light or heavy chain.

45. The method of claim 36, wherein the portion of the antibody comprises a complementarity determining region or a variable region.

46. The method of claim 45, wherein the portion of the antibody comprises a Fab or a single chain antibody.

47. The method of claim 31, wherein the subject is a mammal.

48. The method of claim 47, wherein the mammal is a rodent.

49. The method of claim 47, wherein the mammal is a human.

50. The method of claim 31, wherein the protein comprises soluble extracellular region of CD40 ligand, or variant thereof including conservative substituents, or portion thereof; or soluble extracellular region of CD40, or variant thereof including conservative substituents, or portion thereof.

51. The method of claim 50, wherein the soluble extracellular region of CD40 ligand or CD40 is a monomer.

52. The method of claim 50, wherein the soluble extracellular region of CD40 is an oligomer.

53. The method of claim 50, wherein the protein comprising soluble extracellular region of CD40 or portion thereof or CD40 ligand or portion thereof further comprises an Fc region fused to the extracellular region of CD40 or portion thereof or CD40 ligand or portion thereof.

54. The method of claim 53, wherein the Fc region is capable of binding to protein A or protein G.

55. The method of claim 53, wherein the Fc region comprises IgG, IgA, IgM, IgD, or IgE, or subclasses thereof.

56. The method of claim 55, wherein:
the IgG is IgG_1, IgG_2, IgG_3, or IgG_4; or
the IgA is IgA_1 or IgA_2.

57. The method of claim 31, wherein the agent is

nonprotein.

58. The method of claim 57, wherein the agent is a small molecule.

59. The method of claim 31, wherein the agent is selected from a library of known agents.

60. The method of claim 31, wherein the agent is modified from a known agent.

61. The method of claim 60, wherein the modified agent is designed by structure optimization of a lead inhibitor based on a three-dimensional structure of a complex of soluble extracellular region of CD40 ligand or portion thereof with the lead inhibitor.

62. The method of claim 31, wherein the agent is selected by a screening method, which comprises:

isolating a sample of cells;

culturing the sample under conditions permitting activation of CD40-bearing cells;

contacting the sample with cells expressing a protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession No. HB 10916, or with a protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession No. HB 10916, effective to activate the CD40-bearing cells;

contacting the sample with an amount of the agent effective to inhibit activation of the CD40-bearing cells if the agent is capable of inhibiting

activation of the CD40-bearing cells; and

determining whether the cells expressing the protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession No. HB 10916, or with the protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession No. HB 10916,activate the CD40-bearing cells in the presence of the agent.

63. The method of claim 62, wherein the agent is selected from a library of known agents.

64. The method of claim 63, wherein the known agents are nonprotein agents.

65. A method of treating, in a subject, an inflammatory kidney disease, comprising inhibiting activation by CD40 ligand of renal cells bearing CD40 on the surface of the cells, according to the method of claim 31.

66. The method of claim 65, wherein the inflammatory kidney disease is not initiated by autoantibody deposition in kidney.

67. The method of claim 65, wherein the kidney disease is selected from the group consisting of:

membranous glomerulonephritis;
minimal change disease/acute tubular necrosis;
pauci-immune glomerulonephritis;
focal segmental glomerulosclerosis;
interstitial nephritis;
antitissue antibody-induced glomerular injury;
circulating immune-complex disease;
a glomerulopathy associated with a multisystem

disease;
drug-induced glomerular disease;
renal transplant rejection;
rapidly progressive glomerulonephritis; and
post-streptococcal glomerulonephritis.

68. The method of claim 67, wherein the antitissue antibody-induced glomerular injury is anti-basement membrane antibody disease.

69. The method of claim 67, wherein the circulating immune-complex disease is selected from the group consisting of:
infective endocarditis;
leprosy;
syphilis;
hepatitis B;
malaria; and
a disease associated with an endogenous antigen.

70. The method of claim 69, wherein the endogenous antigen is DNA, thyroglobulin, an autologous immunoglobulin, erythrocyte stroma, a renal tubule antigen, a tumor-specific antigen, or a tumor-associated antigen.

71. The method of claim 67 wherein the glomerulopathy associated with a multisystem disease is selected from the group consisting of:
diabetic nephropathy;
systemic lupus erythematosus;
Goodpasture's disease;
vasculitis;
multiple myeloma;
Waldenström's macroglobulinemia; and
amyloidosis.

72. The method of claim 71, wherein the vasculitis is selected from the group consisting of:

Henoch-Schönlein purpura;
polyarteritis nodosa;
Wegener's granulomatosis; and
cryoglobulinemia.

73. The method of claim 67, wherein the pauci-immune glomerulonephritis is ANCA+ pauci-immune glomerulonephritis, or Wegener's granulomatosis.

74. The method of claim 67, wherein the interstitial nephritis is drug-induced interstitial nephritis.

75. The method of claim 65 wherein the kidney disease affects renal tubules.

76. The method of claim 75, wherein the kidney disease which affects renal tubules is selected from the group consisting of:

a kidney disease associated with a toxin;
a neoplasia;
hypersensitivity nephropathy;
Sjögren's syndrome; and
AIDS.

FIGURE 1A

REMARKS ATOMIC COORDINATES OF CD40L CRYSTAL STRUCTURE IN PDB FORMAT

CRYST	77.170		77.170	90.460	90.00	90.00	120.00	R3		
ATOM	1	N	GLY	116	-7.954	-16.144	22.488	1.00	64.71	A
ATOM	2	HT1	GLY	116	-7.087	-15.852	21.964	1.00	15.00	A
ATOM	3	HT2	GLY	116	-8.082	-17.142	22.242	1.00	15.00	A
ATOM	4	HT3	GLY	116	-8.630	-15.576	21.928	1.00	15.00	A
ATOM	5	CA	GLY	116	-7.927	-15.755	23.928	1.00	64.37	A
ATOM	6	C	GLY	116	-6.990	-16.621	24.780	1.00	64.34	A
ATOM	7	O	GLY	116	-6.968	-17.814	24.563	1.00	64.44	A
ATOM	8	N	ASP	117	-6.238	-16.043	25.740	1.00	64.04	A
ATOM	9	H	ASP	117	-5.617	-16.709	26.170	1.00	15.00	A
ATOM	10	CA	ASP	117	-6.284	-14.616	26.130	1.00	63.57	A
ATOM	11	CB	ASP	117	-5.711	-14.402	27.539	1.00	63.36	A
ATOM	12	CG	ASP	117	-6.518	-15.163	28.574	1.00	63.71	A
ATOM	13	OD1	ASP	117	-6.090	-16.247	28.965	1.00	63.24	A
ATOM	14	OD2	ASP	117	-7.566	-14.668	28.987	1.00	63.29	A
ATOM	15	C	ASP	117	-5.651	-13.585	25.184	1.00	63.31	A
ATOM	16	O	ASP	117	-6.039	-12.427	25.145	1.00	63.35	A
ATOM	17	N	GLN	118	-4.713	-14.090	24.379	1.00	62.72	A
ATOM	18	H	GLN	118	-4.450	-15.040	24.541	1.00	15.00	A
ATOM	19	CA	GLN	118	-4.097	-13.313	23.281	1.00	61.79	A
ATOM	20	CB	GLN	118	-2.918	-14.117	22.687	1.00	62.46	A
ATOM	21	CG	GLN	118	-3.047	-15.659	22.562	1.00	62.95	A
ATOM	22	CD	GLN	118	-4.277	-16.118	21.790	1.00	63.26	A
ATOM	23	OE1	GLN	118	-5.396	-16.000	22.277	1.00	63.43	A
ATOM	24	NE2	GLN	118	-4.044	-16.665	20.601	1.00	63.42	A
ATOM	25	HE21	GLN	118	-4.836	-16.715	19.975	1.00	15.00	A
ATOM	26	HE22	GLN	118	-3.151	-16.995	20.298	1.00	15.00	A
ATOM	27	C	GLN	118	-4.999	-12.841	22.128	1.00	60.59	A
ATOM	28	O	GLN	118	-4.887	-13.379	21.052	1.00	60.79	A
ATOM	29	N	ASN	119	-5.912	-11.901	22.445	1.00	58.61	A
ATOM	30	H	ASN	119	-5.917	-11.600	23.389	1.00	15.00	A
ATOM	31	CA	ASN	119	-6.689	-11.222	21.386	1.00	56.39	A
ATOM	32	CB	ASN	119	-7.947	-11.982	20.936	1.00	56.95	A
ATOM	33	CG	ASN	119	-7.652	-13.352	20.375	1.00	57.45	A
ATOM	34	OD1	ASN	119	-7.941	-14.303	21.084	1.00	58.50	A
ATOM	35	ND2	ASN	119	-7.005	-13.431	19.241	1.00	58.58	A
ATOM	36	HD21	ASN	119	-6.843	-12.617	18.646	1.00	15.00	A
ATOM	37	HD22	ASN	119	-6.740	-14.221	18.684	1.00	15.00	A
ATOM	38	C	ASN	119	-7.053	-9.724	21.571	1.00	53.62	A
ATOM	39	O	ASN	119	-6.746	-8.933	20.694	1.00	56.55	A
ATOM	40	N	PRO	120	-7.737	-9.288	22.698	1.00	50.17	A
ATOM	41	CD	PRO	120	-8.151	-10.129	23.810	1.00	51.90	A
ATOM	42	CA	PRO	120	-8.402	-7.945	22.818	1.00	48.19	A
ATOM	43	CB	PRO	120	-9.191	-8.008	24.117	1.00	47.42	A
ATOM	44	CG	PRO	120	-9.444	-9.493	24.321	1.00	51.93	A
ATOM	45	C	PRO	120	-7.750	-6.524	22.657	1.00	45.59	A
ATOM	46	O	PRO	120	-8.187	-5.516	23.225	1.00	45.37	A
ATOM	47	N	GLN	121	-6.789	-6.458	21.721	1.00	38.52	A
ATOM	48	H	GLN	121	-6.287	-7.704	21.509	1.00	15.00	A
ATOM	49	CA	GLN	121	-6.733	-5.359	20.753	1.00	29.14	A
ATOM	50	CB	GLN	121	-5.454	-5.735	19.971	1.00	26.30	A
ATOM	51	CG	GLN	121	-5.128	-4.943	18.710	1.00	26.84	A
ATOM	52	CD	GLN	121	-4.923	-3.460	18.949	1.00	27.26	A
ATOM	53	OE1	GLN	121	-5.822	-2.668	18.709	1.00	28.66	A
ATOM	54	NE2	GLN	121	-3.717	-3.100	19.341	1.00	33.90	A
ATOM	55	HE21	GLN	121	2.883	-3.614	19.564	1.00	15.00	A
ATOM	56	HE22	GLN	121	-3.442	-2.138	19.204	1.00	15.00	A
ATOM	57	C	GLN	121	-8.065	-5.218	19.903	1.00	26.33	A
ATOM	58	O	GLN	121	-8.905	-6.097	19.834	1.00	21.41	A
ATOM	59	N	ILE	122	-8.288	-4.051	19.272	1.00	21.21	A

FIGURE 1B

ATOM	60	H	ILE	122	-7.600	-3.320	19.337	1.00	18.00	A
ATOM	61	CA	ILE	122	-9.383	-3.952	18.295	1.00	20.82	A
ATOM	62	CB	ILE	122	-10.238	-2.629	18.396	1.00	22.17	A
ATOM	63	CG2	ILE	122	-11.275	-2.428	17.272	1.00	21.61	A
ATOM	64	CG1	ILE	122	-11.076	-2.744	19.668	1.00	24.13	A
ATOM	65	CD1	ILE	122	-11.751	-1.440	20.073	1.00	23.04	A
ATOM	66	C	ILE	122	-8.833	-4.108	16.895	1.00	18.96	A
ATOM	67	O	ILE	122	-8.135	-3.243	16.379	1.00	17.93	A
ATOM	68	N	ALA	123	-9.159	-5.240	16.283	1.00	14.72	A
ATOM	69	H	ALA	123	-9.599	-5.979	16.805	1.00	15.00	A
ATOM	70	CA	ALA	123	-8.656	-5.401	14.917	1.00	14.29	A
ATOM	71	CB	ALA	123	-7.176	-5.868	14.903	1.00	12.83	A
ATOM	72	C	ALA	123	-9.483	-6.315	13.985	1.00	15.66	A
ATOM	73	O	ALA	123	-10.170	-7.261	14.323	1.00	13.58	A
ATOM	74	N	ALA	124	-9.388	-6.009	12.724	1.00	13.45	A
ATOM	75	H	ALA	124	-8.894	-5.185	12.456	1.00	15.00	A
ATOM	76	CA	ALA	124	-10.087	-6.920	11.836	1.00	14.55	A
ATOM	77	CB	ALA	124	-11.486	-6.368	11.446	1.00	11.37	A
ATOM	78	C	ALA	124	-9.271	-7.123	10.563	1.00	13.54	A
ATOM	79	O	ALA	124	-8.501	-6.274	10.129	1.00	16.29	A
ATOM	80	N	HIS	125	-9.544	-8.248	9.937	1.00	11.49	A
ATOM	81	H	HIS	125	-10.100	-8.900	10.426	1.00	15.00	A
ATOM	82	CA	HIS	125	-9.100	-8.524	8.590	1.00	11.51	A
ATOM	83	CB	HIS	125	-7.605	-8.908	8.614	1.00	11.43	A
ATOM	84	CG	HIS	125	-7.119	-9.116	7.205	1.00	7.41	A
ATOM	85	ND1	HIS	125	-6.750	-8.130	6.421	1.00	6.60	A
ATOM	86	HD1	HIS	125	-6.708	-7.168	6.621	1.00	15.00	A
ATOM	87	CD2	HIS	125	-7.075	-10.291	6.456	1.00	12.36	A
ATOM	88	NE2	HIS	125	-6.670	-9.971	5.234	1.00	6.20	A
ATOM	89	CE1	HIS	125	-6.462	-8.646	5.211	1.00	4.48	A
ATOM	90	C	HIS	125	-10.024	-9.570	7.931	1.00	12.63	A
ATOM	91	O	HIS	125	-10.324	-10.650	8.383	1.00	13.14	A
ATOM	92	N	VAL	126	-10.550	-9.129	6.806	1.00	15.65	A
ATOM	93	H	VAL	126	-10.169	-8.286	6.428	1.00	15.00	A
ATOM	94	CA	VAL	126	-11.743	-9.717	6.201	1.00	14.38	A
ATOM	95	CB	VAL	126	-12.877	-8.808	6.675	1.00	13.37	A
ATOM	96	CG1	VAL	126	-13.794	-9.722	7.379	1.00	12.60	A
ATOM	97	CG2	VAL	126	-13.449	-7.663	5.814	1.00	9.61	A
ATOM	98	C	VAL	126	-11.502	-9.971	4.685	1.00	16.03	A
ATOM	99	O	VAL	126	-10.684	-9.297	4.074	1.00	16.42	A
ATOM	100	N	ILE	127	-12.118	-11.013	4.136	1.00	15.99	A
ATOM	101	H	ILE	127	-12.807	-11.481	4.691	1.00	15.00	A
ATOM	102	CA	ILE	127	-11.651	-11.532	2.831	1.00	14.86	A
ATOM	103	CB	ILE	127	-11.414	-13.051	3.002	1.00	17.56	A
ATOM	104	CG2	ILE	127	-11.716	-13.910	1.765	1.00	17.17	A
ATOM	105	CG1	ILE	127	-9.972	-13.316	3.399	1.00	16.47	A
ATOM	106	CD1	ILE	127	-9.705	-12.992	4.864	1.00	19.64	A
ATOM	107	C	ILE	127	-12.691	-11.269	1.765	1.00	18.96	A
ATOM	108	O	ILE	127	-13.898	-11.391	2.016	1.00	20.01	A
ATOM	109	N	SER	128	-12.229	-10.882	0.581	1.00	17.54	A
ATOM	110	H	SER	128	-11.232	-10.871	0.382	1.00	15.00	A
ATOM	111	CA	SER	128	-13.274	-10.667	-0.437	1.00	15.55	A
ATOM	112	CB	SER	128	-12.664	-10.130	-1.706	1.00	18.16	A
ATOM	113	OG	SER	128	-12.205	-11.207	-2.574	1.00	19.90	A
ATOM	114	HG	SER	128	-11.832	-11.931	-2.029	1.00	15.00	A
ATOM	115	C	SER	128	-14.295	-11.761	-0.792	1.00	13.62	A
ATOM	116	O	SER	128	-14.052	-12.960	-0.832	1.00	8.98	A
ATOM	117	N	GLU	129	-15.492	-11.246	-1.027	1.00	13.36	A
ATOM	118	H	GLU	129	-15.661	-10.257	-0.937	1.00	15.00	A
ATOM	119	CA	GLU	129	-16.379	-12.024	-1.840	1.00	17.20	A

FIGURE 1C

ATOM	120	CB	GLU	129	-17.052	-13.117	-1.021	1.00	20.88	A
ATOM	121	CG	GLU	129	-18.092	-12.694	-0.036	1.00	17.91	A
ATOM	122	CD	GLU	129	-18.781	-13.951	0.376	1.00	21.98	A
ATOM	123	OE1	GLU	129	-19.997	-13.932	0.368	1.00	32.23	A
ATOM	124	OE2	GLU	129	-18.150	-14.938	0.734	1.00	33.12	A
ATOM	125	C	GLU	129	-17.371	-11.409	-2.809	1.00	17.71	A
ATOM	126	O	GLU	129	-17.972	-10.389	-2.553	1.00	21.59	A
ATOM	127	N	ALA	130	-17.550	-12.145	-3.914	1.00	20.52	A
ATOM	128	H	ALA	130	-17.136	-13.057	-3.923	1.00	15.00	A
ATOM	129	CA	ALA	130	-18.379	-11.649	-5.019	1.00	23.36	A
ATOM	130	CB	ALA	130	-18.424	-12.633	-6.208	1.00	19.66	A
ATOM	131	C	ALA	130	-19.811	-11.298	-4.570	1.00	26.86	A
ATOM	132	O	ALA	130	-20.519	-12.022	-3.869	1.00	29.40	A
ATOM	133	N	SER	131	-20.198	-10.086	-4.968	1.00	21.70	A
ATOM	134	H	SER	131	-19.515	-9.481	-5.410	1.00	15.00	A
ATOM	135	CA	SER	131	-21.592	-9.782	-4.732	1.00	20.04	A
ATOM	136	CB	SER	131	-21.829	-8.266	-4.787	1.00	20.65	A
ATOM	137	OG	SER	131	-23.182	-8.001	-4.435	1.00	15.24	A
ATOM	138	HG	SER	131	-23.329	-7.069	-4.559	1.00	15.00	A
ATOM	139	C	SER	131	-22.546	-10.501	-5.668	1.00	17.15	A
ATOM	140	O	SER	131	-22.236	-10.853	-6.786	1.00	14.30	A
ATOM	141	N	SER	132	-23.756	-10.731	-5.187	1.00	20.15	A
ATOM	142	H	SER	132	-23.967	-10.586	-4.209	1.00	15.00	A
ATOM	143	CA	SER	132	-24.674	-11.250	-6.218	1.00	21.62	A
ATOM	144	CB	SER	132	-25.266	-12.616	-5.893	1.00	16.00	A
ATOM	145	OG	SER	132	-26.203	-12.324	-4.894	1.00	23.84	A
ATOM	146	HG	SER	132	-26.016	-12.944	-4.179	1.00	15.00	A
ATOM	147	C	SER	132	-25.727	-10.268	-6.671	1.00	20.07	A
ATOM	148	O	SER	132	-26.535	-10.544	-7.547	1.00	20.27	A
ATOM	149	N	LYS	133	-25.606	-9.063	-6.118	1.00	21.87	A
ATOM	150	H	LYS	133	-24.904	-8.969	-5.397	1.00	15.00	A
ATOM	151	CA	LYS	133	-26.406	-7.916	-6.517	1.00	19.23	A
ATOM	152	CB	LYS	133	-27.024	-7.309	-5.256	1.00	23.08	A
ATOM	153	CG	LYS	133	-27.684	-8.364	-4.354	1.00	21.07	A
ATOM	154	CD	LYS	133	-29.174	-8.110	-4.320	1.00	27.36	A
ATOM	155	CE	LYS	133	-29.939	-7.884	-5.670	1.00	30.56	A
ATOM	156	NZ	LYS	133	-31.323	-7.515	-5.345	1.00	21.56	A
ATOM	157	HZ1	LYS	133	-31.862	-7.351	-6.218	1.00	15.00	A
ATOM	158	HZ2	LYS	133	-31.753	-8.299	-4.811	1.00	15.00	A
ATOM	159	HZ3	LYS	133	-31.333	-6.654	-4.760	1.00	15.00	A
ATOM	160	C	LYS	133	-25.579	-6.876	-7.194	1.00	20.10	A
ATOM	161	O	LYS	133	-24.378	-6.801	-7.007	1.00	17.94	A
ATOM	162	N	THR	134	-26.260	-6.052	-7.983	1.00	22.95	A
ATOM	163	H	THR	134	-27.275	-6.130	-8.036	1.00	15.00	A
ATOM	164	CA	THR	134	-25.556	-4.879	-8.561	1.00	27.89	A
ATOM	165	CB	THR	134	-26.498	-4.274	-9.592	1.00	24.59	A
ATOM	166	OG1	THR	134	-26.540	-5.037	-10.792	1.00	24.32	A
ATOM	167	HG1	THR	134	-26.232	-4.411	-11.456	1.00	15.00	A
ATOM	168	CG2	THR	134	-26.044	-2.897	-9.968	1.00	22.97	A
ATOM	169	C	THR	134	-24.987	-3.798	-7.559	1.00	32.51	A
ATOM	170	O	THR	134	-25.658	-3.461	-6.603	1.00	38.43	A
ATOM	171	N	THR	135	-23.717	-3.352	-7.690	1.00	35.98	A
ATOM	172	H	THR	135	-23.292	-3.555	-8.585	1.00	15.00	A
ATOM	173	CA	THR	135	-22.964	-3.469	-6.386	1.00	36.02	A
ATOM	174	CB	THR	135	-21.575	-4.276	-6.534	1.00	36.01	A
ATOM	175	OG1	THR	135	-21.645	-5.388	-7.488	1.00	30.60	A
ATOM	176	HG1	THR	135	-22.255	-6.094	-7.322	1.00	15.00	A
ATOM	177	CG2	THR	135	-20.866	-4.776	-5.264	1.00	35.55	A
ATOM	178	C	THR	135	-22.949	-2.266	-5.404	1.00	30.25	A
ATOM	179	O	THR	135	-23.541	-2.348	-4.331	1.00	28.35	A

FIGURE 1D

ATOM	180	N	SER	136	-22.294	-1.146	-5.776	1.00	23.29	A
ATOM	181	H	SER	136	-22.828	-0.357	-5.460	1.00	15.00	A
ATOM	182	CA	SER	136	-20.857	-1.051	-6.143	1.00	23.04	A
ATOM	183	CB	SER	136	-20.560	0.187	-6.965	1.00	21.03	A
ATOM	184	OG	SER	136	-20.624	1.261	-6.043	1.00	28.21	A
ATOM	185	HG	SER	136	-19.815	1.793	-6.008	1.00	15.00	A
ATOM	186	C	SER	136	-19.553	-1.090	-4.958	1.00	21.77	A
ATOM	187	O	SER	136	-18.630	-1.096	-5.080	1.00	21.94	A
ATOM	188	N	VAL	137	-20.452	-1.227	-3.752	1.00	24.03	A
ATOM	189	H	VAL	137	-21.440	-1.063	-3.705	1.00	15.00	A
ATOM	190	CA	VAL	137	-19.699	-1.632	-2.570	1.00	19.65	A
ATOM	191	CB	VAL	137	-20.218	-1.010	-1.248	1.00	21.14	A
ATOM	192	CG1	VAL	137	-20.419	-1.907	-0.058	1.00	18.16	A
ATOM	193	CG2	VAL	137	-21.322	-0.026	-1.442	1.00	13.49	A
ATOM	194	C	VAL	137	-19.370	-3.116	-2.473	1.00	17.15	A
ATOM	195	O	VAL	137	-20.209	-3.969	-2.593	1.00	16.69	A
ATOM	196	N	LEU	138	-18.077	-3.344	-2.271	1.00	15.84	A
ATOM	197	H	LEU	138	-17.502	-2.528	-2.246	1.00	15.00	A
ATOM	198	CA	LEU	138	-17.507	-4.667	-1.938	1.00	18.21	A
ATOM	199	CB	LEU	138	-15.962	-4.530	-1.791	1.00	13.60	A
ATOM	200	CG	LEU	138	-15.273	-3.854	-2.998	1.00	16.09	A
ATOM	201	CD1	LEU	138	-15.923	-4.379	-4.300	1.00	20.35	A
ATOM	202	CD2	LEU	138	-13.710	-3.936	-2.982	1.00	12.34	A
ATOM	203	C	LEU	138	-18.170	-5.480	-0.772	1.00	16.29	A
ATOM	204	O	LEU	138	-18.498	-4.986	0.301	1.00	12.97	A
ATOM	205	N	GLN	139	-18.345	-6.768	-1.035	1.00	13.04	A
ATOM	206	H	GLN	139	-18.052	-7.078	-1.960	1.00	15.00	A
ATOM	207	CA	GLN	139	-18.757	-7.658	0.013	1.00	15.32	A
ATOM	208	CB	GLN	139	-19.847	-8.678	-0.481	1.00	13.99	A
ATOM	209	CG	GLN	139	-21.068	-7.960	-1.113	1.00	20.85	A
ATOM	210	CD	GLN	139	-21.872	-7.022	-0.193	1.00	22.04	A
ATOM	211	OE1	GLN	139	-22.343	-7.439	0.878	1.00	25.45	A
ATOM	212	NE2	GLN	139	-21.963	-5.739	-0.618	1.00	17.74	A
ATOM	213	HE21	GLN	139	-22.697	-5.181	-0.206	1.00	15.00	A
ATOM	214	HE22	GLN	139	-21.460	-5.326	-1.374	1.00	15.00	A
ATOM	215	C	GLN	139	-17.527	-8.383	0.541	1.00	14.26	A
ATOM	216	O	GLN	139	-16.554	-8.640	-0.144	1.00	14.40	A
ATOM	217	N	TRP	140	-17.647	-8.780	1.805	1.00	12.80	A
ATOM	218	H	TRP	140	-18.433	-8.447	2.297	1.00	15.00	A
ATOM	219	CA	TRP	140	-16.542	-9.500	2.463	1.00	14.03	A
ATOM	220	CB	TRP	140	-15.813	-8.623	3.483	1.00	14.18	A
ATOM	221	CG	TRP	140	-15.467	-7.291	2.823	1.00	8.44	A
ATOM	222	CD2	TRP	140	-14.379	-6.966	1.941	1.00	9.01	A
ATOM	223	CE2	TRP	140	-14.549	-5.625	1.482	1.00	8.40	A
ATOM	224	CE3	TRP	140	-13.215	-7.688	1.581	1.00	10.14	A
ATOM	225	CD1	TRP	140	-16.225	-6.137	2.863	1.00	11.29	A
ATOM	226	NE1	TRP	140	-15.710	-5.150	2.077	1.00	14.27	A
ATOM	227	HE1	TRP	140	-16.121	-4.268	2.010	1.00	15.00	A
ATOM	228	CZ2	TRP	140	-13.640	-5.009	0.590	1.00	8.16	A
ATOM	229	CZ3	TRP	140	-12.292	-7.069	0.713	1.00	13.90	A
ATOM	230	CH2	TRP	140	-12.497	-5.749	0.215	1.00	12.11	A
ATOM	231	C	TRP	140	-17.016	-10.701	3.170	1.00	14.34	A
ATOM	232	O	TRP	140	-18.193	-10.862	3.392	1.00	16.00	A
ATOM	233	N	ALA	141	-16.082	-11.528	3.558	1.00	14.80	A
ATOM	234	H	ALA	141	-15.133	-11.377	3.294	1.00	15.00	A
ATOM	235	CA	ALA	141	-16.489	-12.617	4.394	1.00	15.27	A
ATOM	236	CB	ALA	141	-16.504	-13.920	3.583	1.00	16.97	A
ATOM	237	C	ALA	141	-15.585	-12.761	5.607	1.00	15.90	A
ATOM	238	O	ALA	141	-14.453	-12.338	5.550	1.00	14.25	A
ATOM	239	N	GLU	142	-16.068	-13.366	6.688	1.00	19.74	A

FIGURE 1E

ATOM	240	H	GLU	142	-17.055	-13.574	6.688	1.00	15.00	A
ATOM	241	CA	GLU	142	-18.149	-13.759	7.731	1.00	28.98	A
ATOM	242	CB	GLU	142	-18.794	-13.910	9.117	1.00	31.75	A
ATOM	243	CG	GLU	142	-18.716	-12.456	9.647	1.00	34.08	A
ATOM	244	CD	GLU	142	-16.749	-12.087	10.721	1.00	36.61	A
ATOM	245	OE1	GLU	142	-17.908	-11.888	10.361	1.00	34.72	A
ATOM	246	OE2	GLU	142	-16.404	-11.984	11.886	1.00	30.07	A
ATOM	247	C	GLU	142	-14.200	-14.797	7.193	1.00	33.25	A
ATOM	248	O	GLU	142	-13.156	-14.349	6.737	1.00	41.84	A
ATOM	249	N	LYS	143	-14.577	-16.080	7.084	1.00	34.17	A
ATOM	250	H	LYS	143	-15.432	-16.384	7.492	1.00	15.00	A
ATOM	251	CA	LYS	143	-13.882	-16.854	5.980	1.00	35.31	A
ATOM	252	CB	LYS	143	-14.673	-16.603	4.681	1.00	37.64	A
ATOM	253	CG	LYS	143	-14.300	-17.505	3.531	1.00	47.37	A
ATOM	254	CD	LYS	143	-15.022	-17.284	2.202	1.00	50.37	A
ATOM	255	CE	LYS	143	-14.686	-16.047	1.357	1.00	49.23	A
ATOM	256	NZ	LYS	143	-15.632	-16.097	0.221	1.00	51.67	A
ATOM	257	HZ1	LYS	143	-15.333	-15.445	-0.534	1.00	15.00	A
ATOM	258	HZ2	LYS	143	-15.680	-17.061	-0.177	1.00	15.00	A
ATOM	259	HZ3	LYS	143	-16.564	-15.833	0.585	1.00	15.00	A
ATOM	260	C	LYS	143	-12.330	-16.979	5.637	1.00	32.80	A
ATOM	261	O	LYS	143	-11.831	-18.041	5.276	1.00	35.64	A
ATOM	262	N	GLY	144	-11.522	-15.923	5.637	1.00	28.26	A
ATOM	263	H	GLY	144	-11.718	-14.995	5.910	1.00	15.00	A
ATOM	264	CA	GLY	144	-10.243	-16.458	5.194	1.00	32.94	A
ATOM	265	C	GLY	144	-9.178	-16.862	6.180	1.00	29.93	A
ATOM	266	O	GLY	144	-9.345	-17.454	7.205	1.00	24.67	A
ATOM	267	N	TYR	145	-8.069	-16.270	5.815	1.00	26.37	A
ATOM	268	H	TYR	145	-8.160	-15.729	4.966	1.00	15.00	A
ATOM	269	CA	TYR	145	-7.027	-16.002	6.777	1.00	27.61	A
ATOM	270	CB	TYR	145	-5.708	-15.877	5.947	1.00	37.54	A
ATOM	271	CG	TYR	145	-5.962	-15.774	4.456	1.00	50.95	A
ATOM	272	CD1	TYR	145	-5.682	-14.633	3.706	1.00	53.22	A
ATOM	273	CE1	TYR	145	-6.313	-14.377	2.468	1.00	60.28	A
ATOM	274	CD2	TYR	145	-6.591	-16.847	3.791	1.00	53.11	A
ATOM	275	CE2	TYR	145	-7.207	-16.699	2.551	1.00	56.30	A
ATOM	276	CZ	TYR	145	-7.162	-15.430	1.873	1.00	61.12	A
ATOM	277	OH	TYR	145	-7.812	-15.119	0.665	1.00	62.63	A
ATOM	278	HH	TYR	145	-8.575	-15.686	0.401	1.00	15.00	A
ATOM	279	C	TYR	145	-7.532	-14.762	7.620	1.00	22.41	A
ATOM	280	O	TYR	145	-7.000	-13.677	7.650	1.00	22.68	A
ATOM	281	N	TYR	146	-8.731	-14.884	8.196	1.00	20.39	A
ATOM	282	H	TYR	146	-8.935	-15.824	8.509	1.00	15.00	A
ATOM	283	CA	TYR	146	-9.423	-13.700	8.725	1.00	20.40	A
ATOM	284	CB	TYR	146	-10.886	-13.673	8.306	1.00	22.53	A
ATOM	285	CG	TYR	146	-11.710	-14.460	9.286	1.00	23.02	A
ATOM	286	CD1	TYR	146	-11.635	-15.873	9.236	1.00	26.99	A
ATOM	287	CE1	TYR	146	-12.254	-16.623	10.239	1.00	25.44	A
ATOM	288	CD2	TYR	146	-12.477	-13.766	10.236	1.00	23.45	A
ATOM	289	CE2	TYR	146	-13.150	-14.520	11.205	1.00	26.81	A
ATOM	290	CZ	TYR	146	-13.007	-15.937	11.204	1.00	27.40	A
ATOM	291	OH	TYR	146	-13.647	-16.689	12.170	1.00	31.91	A
ATOM	292	HH	TYR	146	-12.911	-17.080	12.676	1.00	15.00	A
ATOM	293	C	TYR	146	-8.291	-13.419	10.219	1.00	18.79	A
ATOM	294	O	TYR	146	-8.904	-14.232	11.012	1.00	16.13	A
ATOM	295	N	THR	147	-9.596	-12.169	10.556	1.00	17.54	A
ATOM	296	H	THR	147	-9.973	-11.607	9.830	1.00	15.00	A
ATOM	297	CA	THR	147	-9.432	-11.764	11.948	1.00	14.06	A
ATOM	298	CB	THR	147	-8.162	-10.875	12.182	1.00	13.66	A
ATOM	299	OG1	THR	147	-6.912	-11.505	11.856	1.00	12.56	A

FIGURE 1F

ATOM	300	HG1	THR	147	-6.934	-11.899	10.980	1.00	15.00	A
ATOM	301	CG2	THR	147	-8.025	-10.236	13.554	1.00	7.22	A
ATOM	302	C	THR	147	-10.619	-10.925	12.283	1.00	18.60	A
ATOM	303	O	THR	147	-11.044	-10.074	11.496	1.00	16.39	A
ATOM	304	N	MET	148	-11.144	-12.139	13.412	1.00	20.67	A
ATOM	305	H	MET	148	-10.838	-11.988	13.828	1.00	15.00	A
ATOM	306	CA	MET	148	-12.124	-10.311	14.110	1.00	19.71	A
ATOM	307	CB	MET	148	-13.546	-10.702	13.705	1.00	17.89	A
ATOM	308	CG	MET	148	-14.541	-9.580	14.019	1.00	13.53	A
ATOM	309	SD	MET	148	-14.492	-8.149	12.952	1.00	14.69	A
ATOM	310	CE	MET	148	-14.566	-8.928	11.333	1.00	10.10	A
ATOM	311	C	MET	148	-11.915	-10.282	15.639	1.00	21.49	A
ATOM	312	O	MET	148	-12.594	-10.905	16.436	1.00	22.98	A
ATOM	313	N	SER	149	-10.955	-9.412	16.055	1.00	20.58	A
ATOM	314	H	SER	149	-10.516	-8.786	15.406	1.00	15.00	A
ATOM	315	CA	SER	149	-10.388	-9.698	17.419	1.00	19.11	A
ATOM	316	CB	SER	149	-9.174	-8.860	17.792	1.00	22.17	A
ATOM	317	OG	SER	149	-9.540	-7.513	17.975	1.00	14.10	A
ATOM	318	HG	SER	149	-9.571	-7.487	18.934	1.00	15.00	A
ATOM	319	C	SER	149	-11.203	-9.844	18.727	1.00	22.19	A
ATOM	320	O	SER	149	-10.728	-10.267	19.772	1.00	22.95	A
ATOM	321	N	ASN	150	-12.456	-9.322	18.631	1.00	22.71	A
ATOM	322	H	ASN	150	-12.782	-9.247	17.688	1.00	15.00	A
ATOM	323	CA	ASN	150	-13.361	-9.236	19.764	1.00	20.32	A
ATOM	324	CB	ASN	150	-12.734	-8.446	20.955	1.00	21.56	A
ATOM	325	CG	ASN	150	-12.343	-6.962	20.706	1.00	20.71	A
ATOM	326	OD1	ASN	150	-13.059	-6.187	20.119	1.00	17.81	A
ATOM	327	ND2	ASN	150	-11.222	-6.485	21.271	1.00	23.86	A
ATOM	328	HD21	ASN	150	-11.035	-5.521	21.092	1.00	15.00	A
ATOM	329	HD22	ASN	150	-10.670	-7.109	21.821	1.00	15.00	A
ATOM	330	C	ASN	150	-14.644	-8.657	19.256	1.00	20.60	A
ATOM	331	O	ASN	150	-14.718	-8.130	18.148	1.00	20.56	A
ATOM	332	N	ASN	151	-15.637	-8.713	20.149	1.00	23.49	A
ATOM	333	H	ASN	151	-15.455	-9.124	21.038	1.00	15.00	A
ATOM	334	CA	ASN	151	-16.974	-8.080	19.823	1.00	24.71	A
ATOM	335	CB	ASN	151	-18.130	-8.645	20.712	1.00	28.30	A
ATOM	336	CG	ASN	151	-17.959	-8.271	22.173	1.00	33.23	A
ATOM	337	OD1	ASN	151	-17.075	-7.562	22.606	1.00	39.79	A
ATOM	338	ND2	ASN	151	-18.782	-8.838	23.011	1.00	38.32	A
ATOM	339	HD21	ASN	151	-18.553	-8.524	23.928	1.00	15.00	A
ATOM	340	HD22	ASN	151	-19.495	-9.465	22.733	1.00	15.00	A
ATOM	341	C	ASN	151	-17.172	-6.531	19.645	1.00	22.53	A
ATOM	342	O	ASN	151	-18.254	-6.048	19.374	1.00	21.32	A
ATOM	343	N	LEU	152	-16.066	-5.762	19.859	1.00	23.00	A
ATOM	344	H	LEU	152	-15.247	-6.289	20.070	1.00	15.00	A
ATOM	345	CA	LEU	152	-15.924	-4.335	19.525	1.00	18.87	A
ATOM	346	CB	LEU	152	-14.830	-3.700	20.325	1.00	21.77	A
ATOM	347	CG	LEU	152	-14.981	-3.999	21.806	1.00	24.80	A
ATOM	348	CD1	LEU	152	-16.390	-3.645	22.316	1.00	22.82	A
ATOM	349	CD2	LEU	152	-13.847	-3.256	22.556	1.00	23.56	A
ATOM	350	C	LEU	152	-15.565	-3.993	18.094	1.00	17.34	A
ATOM	351	O	LEU	152	-15.590	-2.840	17.708	1.00	13.39	A
ATOM	352	N	VAL	153	-15.267	-5.054	17.309	1.00	18.65	A
ATOM	353	H	VAL	153	-15.156	-5.962	17.716	1.00	15.00	A
ATOM	354	CA	VAL	153	-15.439	-4.910	15.849	1.00	16.81	A
ATOM	355	CB	VAL	153	-14.138	-5.021	14.980	1.00	15.33	A
ATOM	356	CG1	VAL	153	-12.908	-5.718	15.562	1.00	21.22	A
ATOM	357	CG2	VAL	153	-13.775	-3.757	14.287	1.00	16.95	A
ATOM	358	C	VAL	153	-16.405	-5.964	15.301	1.00	13.48	A
ATOM	359	O	VAL	153	-16.363	-7.116	15.647	1.00	13.06	A

FIGURE 1G

ATOM	360	N	THR	154	-17.207	-5.546	14.358	1.00	22.06	A
ATOM	361	H	THR	154	-17.313	-4.568	14.215	1.00	15.00	A
ATOM	362	CA	THR	154	-17.903	-6.600	13.615	1.00	16.28	A
ATOM	363	CB	THR	154	-19.366	-6.747	14.157	1.00	19.51	A
ATOM	364	OG1	THR	154	-19.995	-5.459	14.205	1.00	19.01	A
ATOM	365	HG1	THR	154	-20.577	-5.508	14.949	1.00	15.00	A
ATOM	366	CG2	THR	154	-19.502	-7.288	15.571	1.00	21.62	A
ATOM	367	C	THR	154	-17.997	-6.252	12.107	1.00	18.22	A
ATOM	368	O	THR	154	-17.992	-5.110	11.605	1.00	16.55	A
ATOM	369	N	LEU	155	-18.101	-7.324	11.357	1.00	16.77	A
ATOM	370	H	LEU	155	-18.056	-8.202	11.791	1.00	15.00	A
ATOM	371	CA	LEU	155	-18.514	-7.198	9.967	1.00	17.10	A
ATOM	372	CB	LEU	155	-17.829	-8.353	9.204	1.00	20.04	A
ATOM	373	CG	LEU	155	-17.524	-8.428	7.692	1.00	20.81	A
ATOM	374	CD1	LEU	155	-17.822	-7.159	6.908	1.00	17.03	A
ATOM	375	CD2	LEU	155	-17.912	-9.810	7.139	1.00	12.42	A
ATOM	376	C	LEU	155	-20.055	-7.187	9.904	1.00	20.71	A
ATOM	377	O	LEU	155	-20.712	-8.163	10.217	1.00	18.01	A
ATOM	378	N	GLU	156	-20.593	-5.995	9.561	1.00	19.51	A
ATOM	379	H	GLU	156	-19.959	-5.230	9.440	1.00	15.00	A
ATOM	380	CA	GLU	156	-22.036	-5.888	9.413	1.00	21.95	A
ATOM	381	CB	GLU	156	-22.641	-4.631	10.033	1.00	18.95	A
ATOM	382	CG	GLU	156	-22.098	-4.412	11.436	1.00	27.68	A
ATOM	383	CD	GLU	156	-22.721	-5.194	12.587	1.00	31.62	A
ATOM	384	OE1	GLU	156	-23.347	-6.248	12.367	1.00	33.40	A
ATOM	385	OE2	GLU	156	-22.532	-4.721	13.724	1.00	35.00	A
ATOM	386	C	GLU	156	-22.457	-5.966	7.964	1.00	25.36	A
ATOM	387	O	GLU	156	-21.958	-5.298	7.077	1.00	22.70	A
ATOM	388	N	ASN	157	-23.437	-6.808	7.696	1.00	30.92	A
ATOM	389	H	ASN	157	-23.594	-7.590	8.300	1.00	15.00	A
ATOM	390	CA	ASN	157	-23.804	-6.620	6.300	1.00	33.31	A
ATOM	391	CB	ASN	157	-23.856	-7.970	5.614	1.00	31.69	A
ATOM	392	CG	ASN	157	-23.669	-7.693	4.168	1.00	27.70	A
ATOM	393	OD1	ASN	157	-23.397	-6.593	3.810	1.00	25.89	A
ATOM	394	ND2	ASN	157	-23.893	-8.640	3.275	1.00	41.69	A
ATOM	395	HD21	ASN	157	-24.069	-9.603	3.467	1.00	15.00	A
ATOM	396	HD22	ASN	157	-23.745	-8.295	2.340	1.00	15.00	A
ATOM	397	C	ASN	157	-24.988	-5.658	6.118	1.00	35.08	A
ATOM	398	O	ASN	157	-26.107	-5.949	6.499	1.00	37.06	A
ATOM	399	N	GLY	158	-24.746	-4.443	5.560	1.00	40.03	A
ATOM	400	H	GLY	158	-25.601	-3.952	5.429	1.00	15.00	A
ATOM	401	CA	GLY	158	-23.422	-3.887	5.121	1.00	38.11	A
ATOM	402	C	GLY	158	-23.062	-3.720	3.617	1.00	37.48	A
ATOM	403	O	GLY	158	-23.890	-3.108	2.950	1.00	41.11	A
ATOM	404	N	LYS	159	-21.867	-4.220	3.135	1.00	32.75	A
ATOM	405	H	LYS	159	-21.904	-4.134	2.130	1.00	15.00	A
ATOM	406	CA	LYS	159	-20.828	-4.928	3.962	1.00	27.83	A
ATOM	407	CB	LYS	159	-20.317	-6.122	3.217	1.00	28.17	A
ATOM	408	CG	LYS	159	-19.734	-7.168	4.069	1.00	20.48	A
ATOM	409	CD	LYS	159	-20.533	-8.426	4.192	1.00	29.61	A
ATOM	410	CE	LYS	159	-20.577	-9.191	2.869	1.00	40.41	A
ATOM	411	NZ	LYS	159	-20.796	-10.663	2.986	1.00	40.88	A
ATOM	412	HZ1	LYS	159	-20.739	-11.087	2.035	1.00	15.00	A
ATOM	413	HZ2	LYS	159	-20.070	-11.087	3.600	1.00	15.00	A
ATOM	414	HZ3	LYS	159	-21.738	-10.848	3.389	1.00	15.00	A
ATOM	415	C	LYS	159	-19.688	-4.065	4.463	1.00	26.08	A
ATOM	416	O	LYS	159	-19.023	-3.369	3.696	1.00	28.01	A
ATOM	417	N	GLN	160	-19.683	-3.990	5.807	1.00	18.90	A
ATOM	418	H	GLN	160	-20.211	-4.674	6.319	1.00	15.00	A
ATOM	419	CA	GLN	160	-18.922	-2.929	6.464	1.00	13.89	A

FIGURE 1H

ATOM	420	CB	GLN	160	-19.778	-1.694	6.611	1.00	16.79	A
ATOM	421	CG	GLN	160	-20.881	-1.896	7.633	1.00	18.34	A
ATOM	422	CD	GLN	160	-22.133	-1.166	7.193	1.00	23.97	A
ATOM	423	OE1	GLN	160	-23.088	-0.970	7.893	1.00	31.18	A
ATOM	424	NE2	GLN	160	-22.257	-0.771	5.948	1.00	28.16	A
ATOM	425	HE21	GLN	160	-23.194	-0.420	5.928	1.00	15.00	A
ATOM	426	HE22	GLN	160	-21.624	-0.780	5.186	1.00	15.00	A
ATOM	427	C	GLN	160	-18.313	-3.309	7.777	1.00	12.67	A
ATOM	428	O	GLN	160	-18.838	-4.151	8.498	1.00	14.78	A
ATOM	429	N	LEU	161	-17.187	-2.637	8.085	1.00	11.22	A
ATOM	430	H	LEU	161	-16.767	-2.124	7.340	1.00	15.00	A
ATOM	431	CA	LEU	161	-16.583	-2.870	9.405	1.00	9.71	A
ATOM	432	CB	LEU	161	-15.052	-2.939	9.390	1.00	4.67	A
ATOM	433	CG	LEU	161	-14.438	-4.060	8.559	1.00	7.30	A
ATOM	434	CD1	LEU	161	-14.511	-5.447	9.207	1.00	10.80	A
ATOM	435	CD2	LEU	161	-12.964	-3.794	8.389	1.00	5.48	A
ATOM	436	C	LEU	161	-17.082	-1.836	10.412	1.00	10.17	A
ATOM	437	O	LEU	161	-16.826	-0.657	10.341	1.00	13.36	A
ATOM	438	N	THR	162	-17.848	-2.338	11.375	1.00	16.94	A
ATOM	439	H	THR	162	-18.153	-3.279	11.251	1.00	15.00	A
ATOM	440	CA	THR	162	-18.317	-1.480	12.493	1.00	16.14	A
ATOM	441	CB	THR	162	-19.807	-1.769	12.640	1.00	13.33	A
ATOM	442	OG1	THR	162	-20.339	-1.707	11.308	1.00	16.73	A
ATOM	443	HG1	THR	162	-21.211	-1.254	11.343	1.00	15.00	A
ATOM	444	CG2	THR	162	-20.553	-0.832	13.562	1.00	15.01	A
ATOM	445	C	THR	162	-17.531	-1.547	13.842	1.00	13.28	A
ATOM	446	O	THR	162	-17.358	-2.587	14.449	1.00	20.21	A
ATOM	447	N	VAL	163	-16.994	-0.437	14.282	1.00	14.22	A
ATOM	448	H	VAL	163	-16.859	0.243	13.567	1.00	15.00	A
ATOM	449	CA	VAL	163	-16.326	-0.358	15.586	1.00	15.72	A
ATOM	450	CB	VAL	163	-15.038	0.426	15.428	1.00	11.82	A
ATOM	451	CG1	VAL	163	-15.191	1.944	15.368	1.00	9.87	A
ATOM	452	CG2	VAL	163	-14.229	-0.124	14.245	1.00	18.88	A
ATOM	453	C	VAL	163	-17.193	0.283	16.706	1.00	17.93	A
ATOM	454	O	VAL	163	-18.001	1.180	16.453	1.00	20.25	A
ATOM	455	N	LYS	164	-17.037	-0.232	17.925	1.00	15.44	A
ATOM	456	H	LYS	164	-16.254	-0.858	18.020	1.00	15.00	A
ATOM	457	CA	LYS	164	-17.856	0.138	19.109	1.00	17.33	A
ATOM	458	CB	LYS	164	-18.351	-1.150	19.807	1.00	19.58	A
ATOM	459	CG	LYS	164	-19.214	-1.885	18.759	1.00	23.56	A
ATOM	460	CD	LYS	164	-19.417	-3.410	18.851	1.00	28.85	A
ATOM	461	CE	LYS	164	-20.039	-4.047	17.554	1.00	33.81	A
ATOM	462	NZ	LYS	164	-19.428	-3.681	16.227	1.00	18.98	A
ATOM	463	HZ1	LYS	164	-19.195	-2.667	16.222	1.00	15.00	A
ATOM	464	HZ2	LYS	164	-18.552	-4.223	16.092	1.00	15.00	A
ATOM	465	HZ3	LYS	164	-20.084	-3.888	15.445	1.00	15.00	A
ATOM	466	C	LYS	164	-17.193	1.099	20.056	1.00	15.14	A
ATOM	467	O	LYS	164	-17.712	1.588	21.048	1.00	17.72	A
ATOM	468	N	ARG	165	-15.992	1.428	19.621	1.00	17.49	A
ATOM	469	H	ARG	165	-15.550	0.838	18.932	1.00	15.00	A
ATOM	470	CA	ARG	165	-15.184	2.415	20.325	1.00	20.18	A
ATOM	471	CB	ARG	165	-13.985	1.806	21.049	1.00	24.65	A
ATOM	472	CG	ARG	165	-14.363	0.833	22.126	1.00	29.54	A
ATOM	473	CD	ARG	165	-13.274	1.077	23.145	1.00	38.82	A
ATOM	474	NE	ARG	165	-13.719	1.998	24.186	1.00	43.41	A
ATOM	475	HE	ARG	165	-14.331	1.671	24.908	1.00	15.00	A
ATOM	476	CZ	ARG	165	-13.190	3.250	24.362	1.00	44.06	A
ATOM	477	NH1	ARG	165	-13.406	3.765	25.562	1.00	41.25	A
ATOM	478	HH11	ARG	165	-13.054	4.683	25.763	1.00	15.00	A
ATOM	479	HH12	ARG	165	-13.919	3.249	26.250	1.00	15.00	A

FIGURE 1I

ATOM	480	NH2	ARG	165	-12.485	3.946	23.425	1.00	31.65	A
ATOM	481	HH21	ARG	165	-12.133	4.860	23.623	1.00	15.00	A
ATOM	482	HH22	ARG	165	-12.322	3.527	22.530	1.00	15.00	A
ATOM	483	C	ARG	165	-14.608	3.554	19.510	1.00	17.71	A
ATOM	484	O	ARG	165	-14.018	3.450	18.441	1.00	18.26	A
ATOM	485	N	GLN	166	-14.763	4.687	20.151	1.00	17.43	A
ATOM	486	H	GLN	166	-15.263	4.614	21.007	1.00	15.00	A
ATOM	487	CA	GLN	166	-14.138	5.911	19.698	1.00	19.00	A
ATOM	488	CB	GLN	166	-14.613	7.021	20.610	1.00	23.79	A
ATOM	489	CG	GLN	166	-14.067	8.409	20.386	1.00	34.06	A
ATOM	490	CD	GLN	166	-15.178	9.399	20.659	1.00	45.91	A
ATOM	491	OE1	GLN	166	-15.102	10.492	20.135	1.00	53.64	A
ATOM	492	NE2	GLN	166	-16.202	9.046	21.418	1.00	44.10	A
ATOM	493	HE21	GLN	166	-16.906	9.765	21.443	1.00	15.00	A
ATOM	494	HE22	GLN	166	-16.577	8.287	21.935	1.00	15.00	A
ATOM	495	C	GLN	166	-12.649	5.881	19.644	1.00	17.48	A
ATOM	496	O	GLN	166	-12.029	5.378	20.561	1.00	18.13	A
ATOM	497	N	GLY	167	-12.160	6.478	18.565	1.00	14.83	A
ATOM	498	H	GLY	167	-12.750	6.836	17.850	1.00	15.00	A
ATOM	499	CA	GLY	167	-10.728	6.711	18.557	1.00	16.28	A
ATOM	500	C	GLY	167	-10.044	6.685	17.204	1.00	16.48	A
ATOM	501	O	GLY	167	-10.674	6.601	16.162	1.00	19.19	A
ATOM	502	N	LEU	168	-8.720	6.735	17.209	1.00	17.06	A
ATOM	503	H	LEU	168	-8.311	6.890	18.120	1.00	15.00	A
ATOM	504	CA	LEU	168	-7.925	6.625	15.992	1.00	16.60	A
ATOM	505	CB	LEU	168	-6.600	7.343	16.289	1.00	21.87	A
ATOM	506	CG	LEU	168	-6.247	8.745	15.716	1.00	22.69	A
ATOM	507	CD1	LEU	168	-5.119	9.410	16.539	1.00	21.20	A
ATOM	508	CD2	LEU	168	-7.436	9.617	15.361	1.00	18.38	A
ATOM	509	C	LEU	168	-7.686	5.136	15.604	1.00	14.84	A
ATOM	510	O	LEU	168	-7.282	4.278	16.392	1.00	15.89	A
ATOM	511	N	TYR	169	-7.943	4.873	14.300	1.00	10.57	A
ATOM	512	H	TYR	169	-8.313	5.659	13.807	1.00	15.00	A
ATOM	513	CA	TYR	169	-7.683	3.572	13.656	1.00	5.27	A
ATOM	514	CB	TYR	169	-8.989	3.014	13.230	1.00	5.83	A
ATOM	515	CG	TYR	169	-9.857	2.620	14.423	1.00	6.94	A
ATOM	516	CD1	TYR	169	-10.524	3.598	15.168	1.00	7.40	A
ATOM	517	CE1	TYR	169	-11.390	3.193	16.218	1.00	7.77	A
ATOM	518	CD2	TYR	169	-10.016	1.255	14.744	1.00	8.89	A
ATOM	519	CE2	TYR	169	-10.850	0.841	15.804	1.00	9.40	A
ATOM	520	CZ	TYR	169	-11.563	1.827	16.534	1.00	10.39	A
ATOM	521	OH	TYR	169	-12.443	1.410	17.534	1.00	7.99	A
ATOM	522	HH	TYR	169	-13.009	2.117	17.800	1.00	15.00	A
ATOM	523	C	TYR	169	-6.810	3.642	12.390	1.00	6.72	A
ATOM	524	O	TYR	169	-6.917	4.498	11.557	1.00	9.12	A
ATOM	525	N	TYR	170	-5.899	2.722	12.228	1.00	9.53	A
ATOM	526	H	TYR	170	-5.806	2.081	12.986	1.00	15.00	A
ATOM	527	CA	TYR	170	-5.313	2.511	10.899	1.00	10.01	A
ATOM	528	CB	TYR	170	-3.967	1.797	11.044	1.00	7.46	A
ATOM	529	CG	TYR	170	-3.259	1.636	9.679	1.00	13.45	A
ATOM	530	CD1	TYR	170	-2.680	2.766	9.052	1.00	12.66	A
ATOM	531	CE1	TYR	170	-2.213	2.658	7.738	1.00	10.18	A
ATOM	532	CD2	TYR	170	-3.304	0.385	9.057	1.00	10.90	A
ATOM	533	CE2	TYR	170	-2.891	0.303	7.730	1.00	8.68	A
ATOM	534	CZ	TYR	170	-2.331	1.419	7.124	1.00	9.97	A
ATOM	535	OH	TYR	170	-1.774	1.286	5.859	1.00	17.50	A
ATOM	536	HH	TYR	170	-1.886	0.404	5.514	1.00	15.00	A
ATOM	537	C	TYR	170	-6.279	1.610	10.073	1.00	10.40	A
ATOM	538	O	TYR	170	-6.679	0.500	10.421	1.00	12.52	A
ATOM	539	N	ILE	171	-6.704	2.174	8.968	1.00	12.16	A

FIGURE 1J

ATOM	540	H	ILE	171	-6.475	3.135	8.808	1.00	A
ATOM	541	CA	ILE	171	-7.606	1.430	8.138	1.00	A
ATOM	542	CB	ILE	171	-8.070	1.990	6.812	1.00	A
ATOM	543	CG2	ILE	171	-9.326	3.501	6.677	1.00	A
ATOM	544	CG1	ILE	171	-10.046	1.564	7.214	1.00	A
ATOM	545	CD1	ILE	171	-10.647	0.250	7.619	1.00	A
ATOM	546	C	ILE	171	-7.074	1.234	6.694	1.00	A
ATOM	547	O	ILE	171	-6.453	2.088	6.082	1.00	A
ATOM	548	N	TYR	172	-7.286	0.005	6.216	1.00	A
ATOM	549	H	TYR	172	-7.809	-0.624	6.786	1.00	A
ATOM	550	CA	TYR	172	-6.708	-0.378	4.922	1.00	A
ATOM	551	CB	TYR	172	-5.332	-1.082	5.037	1.00	A
ATOM	552	CG	TYR	172	-5.389	-2.397	5.796	1.00	A
ATOM	553	CD1	TYR	172	-5.342	-2.402	7.216	1.00	A
ATOM	554	CE1	TYR	172	-5.607	-3.620	7.901	1.00	A
ATOM	555	CD2	TYR	172	-5.565	-3.586	5.050	1.00	A
ATOM	556	CE2	TYR	172	-5.829	-4.800	5.740	1.00	A
ATOM	557	CZ	TYR	172	-5.822	-4.808	7.164	1.00	A
ATOM	558	OH	TYR	172	-5.995	-6.002	7.820	1.00	A
ATOM	559	HH	TYR	172	-6.433	-5.843	8.657	1.00	A
ATOM	560	C	TYR	172	-7.605	-1.276	4.106	1.00	A
ATOM	561	O	TYR	172	-8.346	-2.057	4.692	1.00	A
ATOM	562	N	ALA	173	-7.448	-1.141	2.776	1.00	A
ATOM	563	H	ALA	173	-6.751	-0.490	2.503	1.00	A
ATOM	564	CA	ALA	173	-7.940	-2.152	1.836	1.00	A
ATOM	565	CB	ALA	173	-9.300	-1.725	1.292	1.00	A
ATOM	566	C	ALA	173	-7.007	-2.537	0.653	1.00	A
ATOM	567	O	ALA	173	-6.147	-1.806	0.191	1.00	A
ATOM	568	N	GLN	174	-7.244	-3.714	0.109	1.00	A
ATOM	569	H	GLN	174	-7.774	-4.389	0.620	1.00	A
ATOM	570	CA	GLN	174	-6.470	-4.119	-1.070	1.00	A
ATOM	571	CB	GLN	174	-5.582	-5.292	-0.832	1.00	A
ATOM	572	CG	GLN	174	-4.205	-4.727	-1.030	1.00	A
ATOM	573	CD	GLN	174	-3.174	-5.845	-0.979	1.00	A
ATOM	574	OE1	GLN	174	-2.308	-5.899	-0.105	1.00	A
ATOM	575	NE2	GLN	174	-3.268	-6.699	-2.014	1.00	A
ATOM	576	HE21	GLN	174	-2.668	-7.487	-1.970	1.00	A
ATOM	577	HE22	GLN	174	-3.973	-6.621	-2.714	1.00	A
ATOM	578	C	GLN	174	-7.413	-4.644	-2.114	1.00	A
ATOM	579	O	GLN	174	-8.285	-5.434	-1.880	1.00	A
ATOM	580	N	VAL	175	-7.291	-4.107	-3.301	1.00	A
ATOM	581	H	VAL	175	-6.594	-3.401	-3.400	1.00	A
ATOM	582	CA	VAL	175	-8.247	-4.500	-4.323	1.00	A
ATOM	583	CB	VAL	175	-9.319	-3.409	-4.644	1.00	A
ATOM	584	CG1	VAL	175	-10.146	-2.830	-3.495	1.00	A
ATOM	585	CG2	VAL	175	-10.268	-4.061	-5.639	1.00	A
ATOM	586	C	VAL	175	-7.508	-4.859	-5.615	1.00	A
ATOM	587	O	VAL	175	-6.928	-3.997	-6.301	1.00	A
ATOM	588	N	THR	176	-7.563	-6.180	-5.879	1.00	A
ATOM	589	H	THR	176	-7.994	-6.850	-5.250	1.00	A
ATOM	590	CA	THR	176	-7.086	-6.501	-7.222	1.00	A
ATOM	591	CB	THR	176	-5.844	-7.454	-7.256	1.00	A
ATOM	592	OG1	THR	176	-5.948	-8.650	-8.028	1.00	A
ATOM	593	HG1	THR	176	-5.250	-9.253	-7.796	1.00	A
ATOM	594	CG2	THR	176	-5.329	-7.711	-5.867	1.00	A
ATOM	595	C	THR	176	-8.178	-6.700	-8.272	1.00	A
ATOM	596	O	THR	176	-9.326	-7.043	-7.995	1.00	A
ATOM	597	N	PHE	177	-7.855	-6.341	-9.506	1.00	A
ATOM	598	H	PHE	177	-6.920	-6.083	-9.732	1.00	A
ATOM	599	CA	PHE	177	-8.939	-6.511	-10.479	1.00	A

FIGURE 1K

ATOM	600	CB	PHE	177	-9.746	-5.194	-10.589	1.00	20.90	A
ATOM	601	CG	PHE	177	-8.813	-4.034	-10.927	1.00	22.51	A
ATOM	602	CD1	PHE	177	-8.771	-3.548	-12.252	1.00	22.11	A
ATOM	603	CD2	PHE	177	-8.011	-3.422	-9.920	1.00	21.87	A
ATOM	604	CE1	PHE	177	-8.041	-2.387	-12.550	1.00	20.53	A
ATOM	605	CE2	PHE	177	-7.289	-2.247	-10.204	1.00	20.44	A
ATOM	606	CZ	PHE	177	-7.376	-1.713	-11.500	1.00	22.79	A
ATOM	607	C	PHE	177	-8.381	-6.949	-11.800	1.00	22.14	A
ATOM	608	O	PHE	177	-7.219	-6.695	-12.072	1.00	21.60	A
ATOM	609	N	CYS	178	-9.210	-7.555	-12.625	1.00	24.52	A
ATOM	610	H	CYS	178	-10.146	-7.797	-12.370	1.00	15.00	A
ATOM	611	CA	CYS	178	-8.599	-7.849	-13.942	1.00	29.77	A
ATOM	612	CB	CYS	178	-8.501	-9.365	-14.214	1.00	32.06	A
ATOM	613	SG	CYS	178	-7.685	-9.731	-15.792	1.00	35.17	A
ATOM	614	C	CYS	178	-9.323	-7.146	-15.088	1.00	28.41	A
ATOM	615	O	CYS	178	-10.534	-7.247	-15.185	1.00	27.54	A
ATOM	616	N	SER	179	-8.589	-6.393	-15.910	1.00	28.86	A
ATOM	617	H	SER	179	-7.608	-6.271	-15.754	1.00	15.00	A
ATOM	618	CA	SER	179	-9.374	-5.454	-16.704	1.00	29.01	A
ATOM	619	CB	SER	179	-9.379	-4.118	-16.020	1.00	30.82	A
ATOM	620	OG	SER	179	-10.615	-3.492	-16.319	1.00	39.79	A
ATOM	621	HG	SER	179	-10.725	-2.812	-15.667	1.00	15.00	A
ATOM	622	C	SER	179	-9.063	-5.196	-18.165	1.00	31.16	A
ATOM	623	O	SER	179	-7.931	-4.953	-18.537	1.00	28.58	A
ATOM	624	N	ASN	180	-10.083	-5.255	-19.042	1.00	35.32	A
ATOM	625	H	ASN	180	-10.966	-5.700	-18.834	1.00	15.00	A
ATOM	626	CA	ASN	180	-9.782	-4.725	-20.366	1.00	34.74	A
ATOM	627	CB	ASN	180	-10.205	-5.554	-21.589	1.00	37.96	A
ATOM	628	CG	ASN	180	-9.650	-4.980	-22.896	1.00	37.12	A
ATOM	629	OD1	ASN	180	-10.058	-3.947	-23.356	1.00	40.66	A
ATOM	630	ND2	ASN	180	-8.619	-5.536	-23.456	1.00	35.85	A
ATOM	631	HD21	ASN	180	-8.343	-6.475	-23.306	1.00	15.00	A
ATOM	632	HD22	ASN	180	-8.153	-4.891	-24.065	1.00	15.00	A
ATOM	633	C	ASN	180	-10.197	-3.331	-20.588	1.00	36.96	A
ATOM	634	O	ASN	180	-11.314	-2.894	-20.433	1.00	37.89	A
ATOM	635	N	ARG	181	-9.147	-2.699	-21.068	1.00	41.95	A
ATOM	636	H	ARG	181	-8.363	-3.318	-21.141	1.00	15.00	A
ATOM	637	CA	ARG	181	-8.997	-1.313	-21.489	1.00	44.24	A
ATOM	638	CB	ARG	181	-7.563	-1.279	-22.026	1.00	43.43	A
ATOM	639	CG	ARG	181	-6.348	-1.638	-21.101	1.00	45.11	A
ATOM	640	CD	ARG	181	-6.235	-2.853	-20.134	1.00	40.68	A
ATOM	641	NE	ARG	181	-5.064	-2.772	-19.271	1.00	46.11	A
ATOM	642	HE	ARG	181	-4.991	-2.058	-18.578	1.00	15.00	A
ATOM	643	CZ	ARG	181	-4.024	-3.611	-19.432	1.00	49.77	A
ATOM	644	NH1	ARG	181	-2.886	-3.414	-18.790	1.00	54.33	A
ATOM	645	HH11	ARG	181	-2.113	-4.032	-18.918	1.00	15.00	A
ATOM	646	HH12	ARG	181	-2.807	-2.642	-18.161	1.00	15.00	A
ATOM	647	NH2	ARG	181	-4.085	-4.641	-20.247	1.00	54.26	A
ATOM	648	HH21	ARG	181	-3.286	-5.230	-20.354	1.00	15.00	A
ATOM	649	HH22	ARG	181	-4.918	-4.833	-20.761	1.00	15.00	A
ATOM	650	C	ARG	181	-10.049	-0.866	-22.499	1.00	47.10	A
ATOM	651	O	ARG	181	-10.979	-0.112	-22.227	1.00	49.20	A
ATOM	652	N	GLU	182	-9.895	-1.447	-23.690	1.00	49.64	A
ATOM	653	H	GLU	182	-9.201	-2.166	-23.775	1.00	15.00	A
ATOM	654	CA	GLU	182	-10.976	-1.385	-24.676	1.00	52.41	A
ATOM	655	CB	GLU	182	-10.437	-2.020	-25.970	1.00	56.93	A
ATOM	656	CG	GLU	182	-10.932	-1.418	-27.295	1.00	66.05	A
ATOM	657	CD	GLU	182	-10.758	0.116	-27.327	1.00	70.54	A
ATOM	658	OE1	GLU	182	-9.613	0.586	-27.442	1.00	72.98	A
ATOM	659	OE2	GLU	182	-11.778	0.830	-27.244	1.00	72.46	A

FIGURE 1L

ATOM	660	C	GLU	182	-12.388	-1.934	-24.304	1.00	53.00	A
ATOM	661	O	GLU	182	-13.379	-1.492	-24.862	1.00	54.27	A
ATOM	662	N	ALA	183	-12.505	-2.877	-23.335	1.00	52.34	A
ATOM	663	H	ALA	183	-11.676	-3.273	-22.865	1.00	15.00	A
ATOM	664	CA	ALA	183	-13.867	-3.258	-22.899	1.00	50.19	A
ATOM	665	CB	ALA	183	-13.855	-4.721	-22.447	1.00	48.02	A
ATOM	666	C	ALA	183	-14.562	-2.321	-21.867	1.00	50.66	A
ATOM	667	O	ALA	183	-15.712	-1.945	-21.990	1.00	47.77	A
ATOM	668	N	SER	184	-13.773	-1.888	-20.878	1.00	52.95	A
ATOM	669	H	SER	184	-12.826	-2.172	-20.991	1.00	15.00	A
ATOM	670	CA	SER	184	-14.228	-1.043	-19.729	1.00	56.78	A
ATOM	671	CB	SER	184	-13.384	-1.397	-18.481	1.00	53.58	A
ATOM	672	OG	SER	184	-13.975	-2.448	-17.721	1.00	47.46	A
ATOM	673	HG	SER	184	-13.291	-3.019	-17.388	1.00	15.00	A
ATOM	674	C	SER	184	-14.183	0.517	-19.880	1.00	59.95	A
ATOM	675	O	SER	184	-13.913	1.297	-18.964	1.00	65.25	A
ATOM	676	N	SER	185	-14.324	0.995	-21.131	1.00	60.08	A
ATOM	677	H	SER	185	-14.623	0.345	-21.831	1.00	15.00	A
ATOM	678	CA	SER	185	-13.825	2.375	-21.391	1.00	60.12	A
ATOM	679	CB	SER	185	-13.522	2.640	-22.869	1.00	60.49	A
ATOM	680	OG	SER	185	-12.243	2.098	-23.242	1.00	59.80	A
ATOM	681	HG	SER	185	-12.158	1.234	-22.833	1.00	15.00	A
ATOM	682	C	SER	185	-14.580	3.589	-20.885	1.00	59.59	A
ATOM	683	O	SER	185	-15.437	4.159	-21.543	1.00	60.08	A
ATOM	684	N	GLN	186	-14.200	3.990	-19.670	1.00	57.71	A
ATOM	685	H	GLN	186	-13.601	3.376	-19.153	1.00	15.00	A
ATOM	686	CA	GLN	186	-15.121	4.936	-18.993	1.00	57.00	A
ATOM	687	CB	GLN	186	-16.094	4.062	-18.175	1.00	58.66	A
ATOM	688	CG	GLN	186	-15.355	3.354	-17.050	1.00	59.69	A
ATOM	689	CD	GLN	186	-16.369	2.789	-16.088	1.00	59.92	A
ATOM	690	OE1	GLN	186	-17.270	3.513	-15.687	1.00	59.81	A
ATOM	691	NE2	GLN	186	-16.249	1.503	-15.787	1.00	59.63	A
ATOM	692	HE21	GLN	186	-15.492	0.948	-16.113	1.00	15.00	A
ATOM	693	HE22	GLN	186	-16.950	1.119	-15.168	1.00	15.00	A
ATOM	694	C	GLN	186	-14.758	6.290	-18.221	1.00	54.36	A
ATOM	695	O	GLN	186	-15.596	7.198	-18.298	1.00	53.98	A
ATOM	696	N	ALA	187	-13.566	6.424	-17.511	1.00	50.35	A
ATOM	697	H	ALA	187	-13.476	7.274	-16.970	1.00	15.00	A
ATOM	698	CA	ALA	187	-12.388	5.599	-17.832	1.00	43.26	A
ATOM	699	CB	ALA	187	-11.546	6.284	-18.918	1.00	38.95	A
ATOM	700	C	ALA	187	-11.456	4.882	-16.849	1.00	40.48	A
ATOM	701	O	ALA	187	-10.887	3.875	-17.295	1.00	43.24	A
ATOM	702	N	PRO	188	-11.210	5.383	-15.594	1.00	38.66	A
ATOM	703	CD	PRO	188	-11.543	6.687	-15.000	1.00	38.15	A
ATOM	704	CA	PRO	188	-10.220	4.665	-14.751	1.00	35.94	A
ATOM	705	CB	PRO	188	-9.395	5.813	-14.150	1.00	33.99	A
ATOM	706	CG	PRO	188	-10.377	7.000	-14.036	1.00	32.69	A
ATOM	707	C	PRO	188	-10.840	3.783	-13.683	1.00	33.66	A
ATOM	708	O	PRO	188	-11.885	4.062	-13.140	1.00	33.41	A
ATOM	709	N	PHE	189	-10.147	2.695	-13.346	1.00	28.66	A
ATOM	710	H	PHE	189	-9.260	2.508	-13.748	1.00	15.00	A
ATOM	711	CA	PHE	189	-10.721	2.013	-12.171	1.00	26.71	A
ATOM	712	CB	PHE	189	-10.122	0.601	-12.034	1.00	26.21	A
ATOM	713	CG	PHE	189	-10.671	-0.189	-10.849	1.00	22.92	A
ATOM	714	CD1	PHE	189	-10.126	0.005	-9.566	1.00	17.72	A
ATOM	715	CD2	PHE	189	-11.687	-1.165	-11.064	1.00	21.88	A
ATOM	716	CE1	PHE	189	-10.590	-0.815	-8.522	1.00	19.12	A
ATOM	717	CE2	PHE	189	-12.124	-1.995	-10.011	1.00	21.13	A
ATOM	718	CZ	PHE	189	-11.571	-1.806	-8.736	1.00	18.44	A
ATOM	719	C	PHE	189	-10.445	2.815	-10.909	1.00	27.14	A

FIGURE 1M

ATOM	721	C	PHE	189	-9.308	3.244	-10.706	1.00	28.70	A
ATOM	721	N	ILE	190	-11.468	2.964	-10.071	1.00	24.71	A
ATOM	722	H	ILE	190	-12.408	2.786	-10.388	1.00	15.00	A
ATOM	723	CA	ILE	190	-11.193	3.626	-8.786	1.00	24.03	A
ATOM	724	CB	ILE	190	-11.316	5.242	-8.743	1.00	26.86	A
ATOM	725	CG2	ILE	190	-11.892	5.979	-9.997	1.00	19.87	A
ATOM	726	CG1	ILE	190	-11.801	5.888	-7.424	1.00	22.54	A
ATOM	727	CD1	ILE	190	-12.819	7.012	-7.645	1.00	28.56	A
ATOM	728	C	ILE	190	-11.844	2.812	-7.656	1.00	21.97	A
ATOM	729	O	ILE	190	-12.891	2.197	-7.801	1.00	16.30	A
ATOM	730	N	ALA	191	-11.026	2.700	-6.590	1.00	17.21	A
ATOM	731	H	ALA	191	-10.124	3.124	-6.662	1.00	15.00	A
ATOM	732	CA	ALA	191	-11.501	2.195	-5.321	1.00	15.20	A
ATOM	733	CB	ALA	191	-10.730	0.928	-4.968	1.00	14.79	A
ATOM	734	C	ALA	191	-11.439	3.230	-4.206	1.00	17.11	A
ATOM	735	O	ALA	191	-10.467	3.961	-4.052	1.00	14.04	A
ATOM	736	N	SER	192	-12.511	3.245	-3.433	1.00	14.72	A
ATOM	737	H	SER	192	-13.277	2.694	-3.804	1.00	15.00	A
ATOM	738	CA	SER	192	-12.725	4.289	-2.423	1.00	16.69	A
ATOM	739	CB	SER	192	-13.931	5.144	-2.803	1.00	14.83	A
ATOM	740	OG	SER	192	-13.556	5.828	-3.994	1.00	21.23	A
ATOM	741	HG	SER	192	-14.367	5.966	-4.520	1.00	15.00	A
ATOM	742	C	SER	192	-12.980	3.682	-1.069	1.00	17.77	A
ATOM	743	O	SER	192	-13.753	2.738	-0.947	1.00	20.76	A
ATOM	744	N	LEU	193	-12.285	4.209	-0.038	1.00	15.56	A
ATOM	745	H	LEU	193	-11.681	4.959	-0.280	1.00	15.00	A
ATOM	746	CA	LEU	193	-12.510	3.761	1.366	1.00	13.27	A
ATOM	747	CB	LEU	193	-11.195	3.825	2.217	1.00	12.74	A
ATOM	748	CG	LEU	193	-11.051	3.141	3.604	1.00	14.37	A
ATOM	749	CD1	LEU	193	-12.272	2.354	4.116	1.00	14.67	A
ATOM	750	CD2	LEU	193	-10.274	3.986	4.622	1.00	12.64	A
ATOM	751	C	LEU	193	-13.497	4.748	1.911	1.00	11.22	A
ATOM	752	O	LEU	193	-13.188	5.912	1.903	1.00	12.22	A
ATOM	753	N	CYS	194	-14.652	4.326	2.310	1.00	13.66	A
ATOM	754	H	CYS	194	-14.828	3.347	2.276	1.00	15.00	A
ATOM	755	CA	CYS	194	-15.595	5.360	2.713	1.00	14.84	A
ATOM	756	CB	CYS	194	-16.915	5.409	1.918	1.00	17.58	A
ATOM	757	SG	CYS	194	-16.623	5.417	0.165	1.00	16.33	A
ATOM	758	C	CYS	194	-16.046	5.163	4.137	1.00	12.81	A
ATOM	759	O	CYS	194	-15.983	4.072	4.655	1.00	10.34	A
ATOM	760	N	LEU	195	-16.557	6.254	4.697	1.00	14.32	A
ATOM	761	H	LEU	195	-16.541	7.088	4.154	1.00	15.00	A
ATOM	762	CA	LEU	195	-17.039	6.291	6.076	1.00	14.89	A
ATOM	763	CB	LEU	195	-16.195	7.372	6.789	1.00	15.56	A
ATOM	764	CG	LEU	195	-16.571	7.680	8.242	1.00	15.56	A
ATOM	765	CD1	LEU	195	-15.932	8.967	8.762	1.00	13.72	A
ATOM	766	CD2	LEU	195	-16.463	6.448	9.154	1.00	17.25	A
ATOM	767	C	LEU	195	-18.546	6.544	6.209	1.00	13.54	A
ATOM	768	O	LEU	195	-19.038	7.521	5.705	1.00	14.56	A
ATOM	769	N	LYS	196	-19.238	5.667	6.905	1.00	16.36	A
ATOM	770	H	LYS	196	-18.719	4.875	7.197	1.00	15.00	A
ATOM	771	CA	LYS	196	-20.577	5.972	7.405	1.00	21.01	A
ATOM	772	CB	LYS	196	-21.475	4.726	7.146	1.00	22.66	A
ATOM	773	CG	LYS	196	-22.953	4.839	7.590	1.00	31.25	A
ATOM	774	CD	LYS	196	-23.364	4.915	9.104	1.00	40.25	A
ATOM	775	CE	LYS	196	-23.189	3.694	10.060	1.00	43.56	A
ATOM	776	NZ	LYS	196	-23.004	4.158	11.453	1.00	44.46	A
ATOM	777	HZ1	LYS	196	-22.182	4.799	11.467	1.00	15.00	A
ATOM	778	HZ2	LYS	196	-23.847	4.665	11.778	1.00	15.00	A
ATOM	779	HZ3	LYS	196	-23.807	3.334	12.066	1.00	15.00	A

FIGURE 1N

ATOM	781	C	LYS	196	-20.478	6.290	8.899	1.00	19.25	A
ATOM	782	O	LYS	196	-20.194	5.434	9.714	1.00	18.38	A
ATOM	783	N	SER	197	-20.664	7.534	9.272	1.00	21.63	A
ATOM	784	H	SER	197	-20.891	8.247	8.615	1.00	15.00	A
ATOM	785	CA	SER	197	-20.752	7.701	10.709	1.00	24.87	A
ATOM	786	CB	SER	197	-19.898	8.878	11.207	1.00	25.62	A
ATOM	787	OG	SER	197	-19.563	8.687	12.568	1.00	32.22	A
ATOM	788	HG	SER	197	-18.795	8.210	12.611	1.00	15.00	A
ATOM	789	C	SER	197	-22.216	7.810	11.218	1.00	26.33	A
ATOM	790	O	SER	197	-23.078	8.303	10.497	1.00	26.57	A
ATOM	791	N	PRO	198	-22.534	7.274	12.407	1.00	26.77	A
ATOM	792	CD	PRO	198	-21.649	6.526	13.301	1.00	32.92	A
ATOM	793	CA	PRO	198	-23.919	7.381	12.913	1.00	28.73	A
ATOM	794	CB	PRO	198	-23.784	6.789	14.318	1.00	32.89	A
ATOM	795	CG	PRO	198	-22.289	6.726	14.659	1.00	33.55	A
ATOM	796	C	PRO	198	-24.591	8.789	12.847	1.00	26.60	A
ATOM	797	O	PRO	198	-24.035	9.817	13.242	1.00	20.20	A
ATOM	798	N	GLY	199	-25.729	8.773	12.119	1.00	25.75	A
ATOM	799	H	GLY	199	-26.170	7.857	12.057	1.00	15.00	A
ATOM	800	CA	GLY	199	-26.486	10.003	11.790	1.00	26.91	A
ATOM	801	C	GLY	199	-25.821	10.971	10.816	1.00	28.98	A
ATOM	802	O	GLY	199	-26.084	12.151	10.797	1.00	31.05	A
ATOM	803	N	ARG	200	-24.898	10.464	10.001	1.00	30.15	A
ATOM	804	H	ARG	200	-24.629	9.519	10.165	1.00	15.00	A
ATOM	805	CA	ARG	200	-24.140	11.384	9.166	1.00	28.98	A
ATOM	806	CB	ARG	200	-22.749	11.590	9.783	1.00	33.16	A
ATOM	807	CG	ARG	200	-22.739	12.290	11.162	1.00	38.34	A
ATOM	808	CD	ARG	200	-21.327	12.530	11.705	1.00	42.14	A
ATOM	809	NE	ARG	200	-21.292	12.875	13.131	1.00	43.64	A
ATOM	810	HE	ARG	200	-21.327	13.831	13.424	1.00	15.00	A
ATOM	811	CZ	ARG	200	-21.138	11.896	14.051	1.00	46.40	A
ATOM	812	NH1	ARG	200	-21.219	10.603	13.733	1.00	46.31	A
ATOM	813	HH11	ARG	200	-21.104	9.910	14.445	1.00	15.00	A
ATOM	814	HH12	ARG	200	-21.394	10.320	12.789	1.00	15.00	A
ATOM	815	NH2	ARG	200	-20.901	12.226	15.311	1.00	46.65	A
ATOM	816	HH21	ARG	200	-20.847	13.193	15.566	1.00	15.00	A
ATOM	817	HH22	ARG	200	-20.785	11.510	16.002	1.00	15.00	A
ATOM	818	C	ARG	200	-24.084	10.967	7.710	1.00	27.77	A
ATOM	819	O	ARG	200	-24.264	9.791	7.449	1.00	28.21	A
ATOM	820	N	PHE	201	-23.853	11.926	6.792	1.00	30.83	A
ATOM	821	H	PHE	201	-23.513	12.821	7.126	1.00	15.00	A
ATOM	822	CA	PHE	201	-24.016	11.708	5.339	1.00	34.17	A
ATOM	823	CB	PHE	201	-23.851	12.996	4.572	1.00	31.58	A
ATOM	824	CG	PHE	201	-25.154	13.730	4.614	1.00	34.85	A
ATOM	825	CD1	PHE	201	-25.174	15.062	5.081	1.00	37.56	A
ATOM	826	CD2	PHE	201	-26.335	13.081	4.190	1.00	37.89	A
ATOM	827	CE1	PHE	201	-26.397	15.749	5.182	1.00	36.91	A
ATOM	828	CE2	PHE	201	-27.566	13.762	4.280	1.00	38.98	A
ATOM	829	CZ	PHE	201	-27.572	15.065	4.815	1.00	37.61	A
ATOM	830	C	PHE	201	-23.277	10.605	4.545	1.00	39.40	A
ATOM	831	O	PHE	201	-23.853	10.034	3.604	1.00	45.71	A
ATOM	832	N	GLU	202	-22.031	10.316	5.034	1.00	35.75	A
ATOM	833	H	GLU	202	-21.878	10.753	5.925	1.00	15.00	A
ATOM	834	CA	GLU	202	-20.964	9.564	4.318	1.00	34.52	A
ATOM	835	CB	GLU	202	-21.295	8.540	3.234	1.00	33.66	A
ATOM	836	CG	GLU	202	-21.924	7.245	3.713	1.00	40.61	A
ATOM	837	CD	GLU	202	-22.647	6.505	2.561	1.00	46.12	A
ATOM	838	OE1	GLU	202	-23.461	5.613	2.886	1.00	46.89	A
ATOM	839	OE2	GLU	202	-22.417	6.814	1.370	1.00	45.63	A
ATOM	840	C	GLU	202	-19.924	10.450	3.717	1.00	29.99	A

FIGURE 10

ATOM	840	C	GLU	202	-20.197	11.867	3.300	1.00	30.76	A
ATOM	841	N	ARG	203	-19.728	9.897	3.856	1.00	26.88	A
ATOM	842	H	ARG	203	-18.690	8.998	4.285	1.00	18.00	A
ATOM	843	CA	ARG	203	-17.539	10.603	3.358	1.00	21.86	A
ATOM	844	CB	ARG	203	-16.819	11.410	4.457	1.00	27.00	A
ATOM	845	CG	ARG	203	-17.681	12.187	5.467	1.00	37.32	A
ATOM	846	CD	ARG	203	-16.894	13.213	6.339	1.00	48.09	A
ATOM	847	NE	ARG	203	-15.911	12.667	7.308	1.00	56.90	A
ATOM	848	HE	ARG	203	-16.240	12.433	8.223	1.00	15.00	A
ATOM	849	CZ	ARG	203	-14.572	12.475	7.001	1.00	66.77	A
ATOM	850	NH1	ARG	203	-13.702	12.002	7.911	1.00	68.44	A
ATOM	851	HH11	ARG	203	-12.745	11.829	7.666	1.00	15.00	A
ATOM	852	HH12	ARG	203	-14.016	11.822	8.845	1.00	15.00	A
ATOM	853	NH2	ARG	203	-14.084	12.716	5.766	1.00	67.68	A
ATOM	854	HH21	ARG	203	-14.670	13.108	5.060	1.00	15.00	A
ATOM	855	HH22	ARG	203	-13.143	12.499	5.544	1.00	15.00	A
ATOM	856	C	ARG	203	-16.517	9.633	2.678	1.00	17.71	A
ATOM	857	O	ARG	203	-16.375	8.418	2.931	1.00	7.69	A
ATOM	858	N	ILE	204	-15.789	10.253	1.791	1.00	14.42	A
ATOM	859	H	ILE	204	-15.915	11.228	1.561	1.00	15.00	A
ATOM	860	CA	ILE	204	-14.662	9.482	1.353	1.00	18.32	A
ATOM	861	CB	ILE	204	-14.520	9.392	-0.231	1.00	24.52	A
ATOM	862	CG2	ILE	204	-15.820	9.529	-1.069	1.00	21.85	A
ATOM	863	CG1	ILE	204	-13.439	10.195	-0.949	1.00	26.35	A
ATOM	864	CD1	ILE	204	-13.992	11.231	-1.961	1.00	36.33	A
ATOM	865	C	ILE	204	-13.387	9.819	2.153	1.00	16.58	A
ATOM	866	O	ILE	204	-13.070	10.956	2.457	1.00	18.63	A
ATOM	867	N	LEU	205	-12.718	8.725	2.571	1.00	13.32	A
ATOM	868	H	LEU	205	-13.142	7.853	2.321	1.00	15.00	A
ATOM	869	CA	LEU	205	-11.467	8.829	3.322	1.00	10.01	A
ATOM	870	CB	LEU	205	-11.440	7.688	4.382	1.00	6.66	A
ATOM	871	CG	LEU	205	-12.571	7.727	5.441	1.00	7.99	A
ATOM	872	CD1	LEU	205	-12.722	9.088	6.089	1.00	8.78	A
ATOM	873	CD2	LEU	205	-12.419	6.720	6.582	1.00	8.08	A
ATOM	874	C	LEU	205	-10.268	8.811	2.377	1.00	9.75	A
ATOM	875	O	LEU	205	-9.416	9.655	2.320	1.00	10.25	A
ATOM	876	N	LEU	206	-10.252	7.769	1.562	1.00	10.28	A
ATOM	877	H	LEU	206	-10.991	7.119	1.684	1.00	15.00	A
ATOM	878	CA	LEU	206	-9.166	7.555	0.610	1.00	10.02	A
ATOM	879	CB	LEU	206	-8.249	6.384	0.990	1.00	11.94	A
ATOM	880	CG	LEU	206	-7.001	6.527	1.859	1.00	14.40	A
ATOM	881	CD1	LEU	206	-7.094	5.595	3.074	1.00	14.49	A
ATOM	882	CD2	LEU	206	-6.531	7.958	2.151	1.00	8.78	A
ATOM	883	C	LEU	206	-9.756	7.071	-0.697	1.00	11.91	A
ATOM	884	O	LEU	206	-10.792	6.406	-0.778	1.00	10.67	A
ATOM	885	N	ARG	207	-9.005	7.428	-1.720	1.00	8.06	A
ATOM	886	H	ARG	207	-8.196	7.992	-1.553	1.00	15.00	A
ATOM	887	CA	ARG	207	-9.309	6.823	-2.992	1.00	10.45	A
ATOM	888	CB	ARG	207	-9.974	7.790	-3.904	1.00	8.71	A
ATOM	889	CG	ARG	207	-11.258	8.270	-3.357	1.00	15.68	A
ATOM	890	CD	ARG	207	-11.652	9.459	-4.163	1.00	22.25	A
ATOM	891	NE	ARG	207	-12.670	9.192	-5.171	1.00	29.59	A
ATOM	892	HE	ARG	207	-13.115	8.300	-5.249	1.00	15.00	A
ATOM	893	CZ	ARG	207	-13.063	10.272	-5.919	1.00	40.09	A
ATOM	894	NH1	ARG	207	-12.482	11.498	-5.813	1.00	36.32	A
ATOM	895	HH11	ARG	207	-12.813	12.246	-6.391	1.00	15.00	A
ATOM	896	HH12	ARG	207	-11.737	11.651	-5.165	1.00	15.00	A
ATOM	897	NH2	ARG	207	-14.067	10.111	-6.773	1.00	40.86	A
ATOM	898	HH21	ARG	207	-14.392	10.877	-7.329	1.00	15.00	A
ATOM	899	HH22	ARG	207	-14.498	9.207	-6.853	1.00	15.00	A

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ATOM	900	C	ARG	207	-8.044	6.456	-3.741	1.00	12.59	A
ATOM	901	O	ARG	207	-7.053	7.180	-3.787	1.00	15.58	A
ATOM	902	N	ALA	208	-8.096	5.359	-4.465	1.00	17.06	A
ATOM	903	H	ALA	208	-8.879	4.758	-4.355	1.00	15.00	A
ATOM	904	CA	ALA	208	-7.025	5.128	-5.465	1.00	17.00	A
ATOM	905	CB	ALA	208	-6.052	4.020	-5.072	1.00	14.69	A
ATOM	906	C	ALA	208	-7.544	4.830	-6.854	1.00	20.46	A
ATOM	907	O	ALA	208	-8.438	4.020	-7.057	1.00	21.89	A
ATOM	908	N	ALA	209	-6.986	5.586	-7.808	1.00	26.22	A
ATOM	909	H	ALA	209	-6.280	6.235	-7.533	1.00	15.00	A
ATOM	910	CA	ALA	209	-7.253	5.208	-9.196	1.00	28.06	A
ATOM	911	CB	ALA	209	-7.702	6.380	-10.069	1.00	27.10	A
ATOM	912	C	ALA	209	-6.075	4.461	-9.832	1.00	32.54	A
ATOM	913	O	ALA	209	-4.895	4.726	-9.593	1.00	33.00	A
ATOM	914	N	ASN	210	-6.502	3.491	-10.634	1.00	32.21	A
ATOM	915	H	ASN	210	-7.466	3.249	-10.531	1.00	15.00	A
ATOM	916	CA	ASN	210	-5.674	2.893	-11.662	1.00	36.00	A
ATOM	917	CB	ASN	210	-5.366	1.446	-11.355	1.00	39.53	A
ATOM	918	CG	ASN	210	-4.463	1.366	-10.154	1.00	42.59	A
ATOM	919	OD1	ASN	210	-4.285	2.273	-9.342	1.00	39.26	A
ATOM	920	ND2	ASN	210	-3.951	0.165	-10.055	1.00	41.77	A
ATOM	921	HD21	ASN	210	-3.990	-0.479	-10.817	1.00	15.00	A
ATOM	922	HD22	ASN	210	-3.364	-0.081	-9.279	1.00	15.00	A
ATOM	923	C	ASN	210	-6.299	2.931	-13.043	1.00	36.95	A
ATOM	924	O	ASN	210	-7.492	2.752	-13.259	1.00	36.93	A
ATOM	925	N	THR	211	-5.447	3.168	-14.013	1.00	37.83	A
ATOM	926	H	THR	211	-4.484	3.377	-13.821	1.00	15.00	A
ATOM	927	CA	THR	211	-6.119	3.224	-15.314	1.00	41.27	A
ATOM	928	CB	THR	211	-5.325	4.158	-16.268	1.00	44.53	A
ATOM	929	OG1	THR	211	-6.076	4.506	-17.438	1.00	49.34	A
ATOM	930	HG1	THR	211	-6.032	5.493	-17.508	1.00	15.00	A
ATOM	931	CG2	THR	211	-3.926	3.604	-16.581	1.00	46.08	A
ATOM	932	C	THR	211	-6.434	1.833	-15.878	1.00	39.17	A
ATOM	933	O	THR	211	-5.822	0.863	-15.475	1.00	36.48	A
ATOM	934	N	HIS	212	-7.416	1.718	-16.789	1.00	37.14	A
ATOM	935	H	HIS	212	-8.106	2.438	-16.878	1.00	15.00	A
ATOM	936	CA	HIS	212	-7.294	0.454	-17.529	1.00	33.23	A
ATOM	937	CB	HIS	212	-8.680	-0.012	-18.082	1.00	27.73	A
ATOM	938	CG	HIS	212	-9.856	0.060	-17.111	1.00	24.58	A
ATOM	939	ND1	HIS	212	-10.862	0.967	-17.161	1.00	24.59	A
ATOM	940	HD1	HIS	212	-11.000	1.702	-17.794	1.00	15.00	A
ATOM	941	CD2	HIS	212	-10.049	-0.723	-15.985	1.00	20.65	A
ATOM	942	NE2	HIS	212	-11.154	-0.265	-15.383	1.00	24.01	A
ATOM	943	CE1	HIS	212	-11.665	0.780	-16.092	1.00	17.59	A
ATOM	944	C	HIS	212	-6.257	0.633	-18.683	1.00	38.31	A
ATOM	945	O	HIS	212	-5.363	-0.132	-18.923	1.00	33.92	A
ATOM	946	N	SER	213	-6.444	1.737	-19.443	1.00	46.63	A
ATOM	947	H	SER	213	-7.156	2.323	-19.055	1.00	15.00	A
ATOM	948	CA	SER	213	-5.705	2.177	-20.675	1.00	53.91	A
ATOM	949	CB	SER	213	-4.272	2.704	-20.400	1.00	52.61	A
ATOM	950	OG	SER	213	-3.266	1.697	-20.547	1.00	53.97	A
ATOM	951	HG	SER	213	-3.363	2.064	-19.823	1.00	15.00	A
ATOM	952	C	SER	213	-5.844	1.508	-22.097	1.00	60.03	A
ATOM	953	O	SER	213	-5.005	0.811	-22.682	1.00	61.19	A
ATOM	954	N	SER	214	-7.043	1.803	-22.686	1.00	64.96	A
ATOM	955	H	SER	214	-7.705	2.322	-22.146	1.00	15.00	A
ATOM	956	CA	SER	214	-7.463	1.456	-24.094	1.00	69.62	A
ATOM	957	CB	SER	214	-8.727	2.218	-24.495	1.00	67.82	A
ATOM	958	OG	SER	214	-9.563	2.257	-23.336	1.00	67.64	A
ATOM	959	HG	SER	214	-10.468	2.398	-23.623	1.00	15.00	A

FIGURE 1Q

ATOM	960	C	SER	214	-6.818	1.887	-25.300	1.00	72.08	A
ATOM	961	O	SER	214	-6.202	2.663	-25.686	1.00	73.48	A
ATOM	962	N	ALA	215	-6.175	0.409	-25.899	1.00	73.38	A
ATOM	963	H	ALA	215	-5.456	0.596	-26.565	1.00	15.00	A
ATOM	964	CA	ALA	215	-6.858	-0.915	-25.753	1.00	72.62	A
ATOM	965	CB	ALA	215	-7.199	-1.505	-27.138	1.00	73.08	A
ATOM	966	C	ALA	215	-6.331	-2.148	-24.983	1.00	72.11	A
ATOM	967	O	ALA	215	-7.020	-3.161	-25.069	1.00	72.74	A
ATOM	968	N	LYS	216	-5.153	-2.076	-24.282	1.00	70.17	A
ATOM	969	H	LYS	216	-4.747	-1.165	-24.199	1.00	15.00	A
ATOM	970	CA	LYS	216	-4.482	-3.256	-23.626	1.00	67.38	A
ATOM	971	CB	LYS	216	-3.458	-2.691	-22.648	1.00	65.30	A
ATOM	972	CG	LYS	216	-2.217	-2.107	-23.321	1.00	66.86	A
ATOM	973	CD	LYS	216	-1.419	-3.149	-24.134	1.00	68.81	A
ATOM	974	CE	LYS	216	-0.082	-2.674	-24.740	1.00	67.51	A
ATOM	975	NZ	LYS	216	0.483	-3.722	-25.598	1.00	67.80	A
ATOM	976	HZ1	LYS	216	0.620	-4.590	-25.041	1.00	15.00	A
ATOM	977	HZ2	LYS	216	-0.168	-3.914	-26.385	1.00	15.00	A
ATOM	978	HZ3	LYS	216	1.401	-3.406	-25.973	1.00	15.00	A
ATOM	979	C	LYS	216	-5.321	-4.441	-22.993	1.00	66.99	A
ATOM	980	O	LYS	216	-6.462	-4.266	-22.575	1.00	69.90	A
ATOM	981	N	PRO	217	-4.835	-5.724	-22.952	1.00	65.06	A
ATOM	982	CD	PRO	217	-3.525	-6.262	-23.308	1.00	67.91	A
ATOM	983	CA	PRO	217	-5.792	-6.827	-22.626	1.00	62.80	A
ATOM	984	CB	PRO	217	-5.285	-8.004	-23.464	1.00	64.33	A
ATOM	985	CG	PRO	217	-3.755	-7.799	-23.338	1.00	69.63	A
ATOM	986	C	PRO	217	-5.837	-7.237	-21.150	1.00	59.77	A
ATOM	987	O	PRO	217	-4.747	-7.318	-20.589	1.00	58.81	A
ATOM	988	N	CYS	218	-7.115	-7.516	-20.627	1.00	55.45	A
ATOM	989	H	CYS	218	-7.874	-7.287	-21.233	1.00	15.00	A
ATOM	990	CA	CYS	218	-7.433	-7.929	-19.210	1.00	46.55	A
ATOM	991	CB	CYS	218	-8.105	-9.289	-19.079	1.00	44.69	A
ATOM	992	SG	CYS	218	-8.855	-9.822	-17.460	1.00	43.11	A
ATOM	993	C	CYS	218	-6.265	-7.994	-18.263	1.00	43.24	A
ATOM	994	O	CYS	218	-5.720	-9.026	-17.959	1.00	44.68	A
ATOM	995	N	GLY	219	-5.853	-6.820	-17.876	1.00	40.28	A
ATOM	996	H	GLY	219	-6.328	-5.961	-18.059	1.00	15.00	A
ATOM	997	CA	GLY	219	-4.659	-6.828	-17.070	1.00	36.27	A
ATOM	998	C	GLY	219	-5.017	-7.080	-15.643	1.00	33.86	A
ATOM	999	O	GLY	219	-5.906	-6.452	-15.097	1.00	34.90	A
ATOM	1000	N	GLN	220	-4.313	-7.996	-15.023	1.00	33.15	A
ATOM	1001	H	GLN	220	-3.835	-8.684	-15.580	1.00	15.00	A
ATOM	1002	CA	GLN	220	-4.448	-7.929	-13.578	1.00	29.92	A
ATOM	1003	CB	GLN	220	-4.298	-9.282	-12.936	1.00	27.81	A
ATOM	1004	CG	GLN	220	-5.380	-9.340	-11.883	1.00	30.94	A
ATOM	1005	CD	GLN	220	-5.285	-10.631	-11.132	1.00	36.37	A
ATOM	1006	OE1	GLN	220	-4.216	-10.969	-10.661	1.00	38.47	A
ATOM	1007	NE2	GLN	220	-6.425	-11.296	-10.977	1.00	37.61	A
ATOM	1008	HE21	GLN	220	-6.295	-12.235	-10.667	1.00	15.00	A
ATOM	1009	HE22	GLN	220	-7.373	-11.036	-11.200	1.00	15.00	A
ATOM	1010	C	GLN	220	-3.666	-6.845	-12.859	1.00	27.48	A
ATOM	1011	O	GLN	220	-2.461	-6.694	-12.999	1.00	27.61	A
ATOM	1012	N	GLN	221	-4.438	-6.040	-12.110	1.00	25.10	A
ATOM	1013	H	GLN	221	-5.433	-6.174	-12.143	1.00	15.00	A
ATOM	1014	CA	GLN	221	-3.803	-4.929	-11.387	1.00	22.41	A
ATOM	1015	CB	GLN	221	-4.077	-3.528	-11.949	1.00	22.12	A
ATOM	1016	CG	GLN	221	-3.284	-3.029	-13.163	1.00	32.16	A
ATOM	1017	CD	GLN	221	-3.795	-1.637	-13.405	1.00	34.69	A
ATOM	1018	OE1	GLN	221	-3.746	-0.763	-12.558	1.00	42.12	A
ATOM	1019	NE2	GLN	221	-4.648	-1.507	-14.398	1.00	34.93	A

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ATOM	1020	HE21	GLN	221	-4.981	-2.187	-15.042	1.00	15.00	A
ATOM	1021	HE22	GLN	221	-4.844	-0.881	-14.575	1.00	15.00	A
ATOM	1022	C	GLN	221	-4.227	-4.913	-9.948	1.00	19.54	A
ATOM	1023	O	GLN	221	-5.300	-5.381	-9.611	1.00	19.46	A
ATOM	1024	N	SER	222	-3.374	-4.330	-9.223	1.00	18.22	A
ATOM	1025	H	SER	222	-2.442	-4.098	-9.441	1.00	15.00	A
ATOM	1026	CA	SER	222	-3.851	-4.120	-7.752	1.00	19.45	A
ATOM	1027	CB	SER	222	-3.104	-4.947	-6.691	1.00	19.99	A
ATOM	1028	OG	SER	222	-3.096	-6.339	-7.053	1.00	24.64	A
ATOM	1029	HG	SER	222	-2.651	-6.336	-7.904	1.00	15.00	A
ATOM	1030	C	SER	222	-3.731	-2.688	-7.330	1.00	24.09	A
ATOM	1031	O	SER	222	-2.992	-1.929	-7.944	1.00	29.41	A
ATOM	1032	N	ILE	223	-4.534	-2.386	-6.283	1.00	22.81	A
ATOM	1033	H	ILE	223	-5.172	-3.127	-6.074	1.00	15.00	A
ATOM	1034	CA	ILE	223	-4.567	-1.122	-5.530	1.00	21.06	A
ATOM	1035	CB	ILE	223	-5.970	-0.490	-5.852	1.00	19.87	A
ATOM	1036	CG2	ILE	223	-6.564	0.315	-4.673	1.00	16.59	A
ATOM	1037	CG1	ILE	223	-5.911	0.278	-7.188	1.00	15.22	A
ATOM	1038	CD1	ILE	223	-7.229	0.868	-7.709	1.00	20.54	A
ATOM	1039	C	ILE	223	-4.367	-1.446	-4.007	1.00	21.62	A
ATOM	1040	O	ILE	223	-5.098	-2.269	-3.444	1.00	19.58	A
ATOM	1041	N	HIS	224	-3.429	-0.767	-3.340	1.00	19.73	A
ATOM	1042	H	HIS	224	-2.794	-0.230	-3.899	1.00	15.00	A
ATOM	1043	CA	HIS	224	-3.497	-0.671	-1.858	1.00	16.45	A
ATOM	1044	CB	HIS	224	-2.164	-1.183	-1.227	1.00	18.74	A
ATOM	1045	CG	HIS	224	-2.182	-1.442	0.296	1.00	14.92	A
ATOM	1046	ND1	HIS	224	-2.479	-2.628	0.682	1.00	15.33	A
ATOM	1047	HD1	HIS	224	-2.667	-3.515	0.505	1.00	15.00	A
ATOM	1048	CD2	HIS	224	-1.964	-0.524	1.310	1.00	13.79	A
ATOM	1049	NE2	HIS	224	-2.137	-1.127	2.517	1.00	10.52	A
ATOM	1050	CE1	HIS	224	-2.458	-2.411	2.232	1.00	11.70	A
ATOM	1051	C	HIS	224	-3.914	0.699	-1.284	1.00	15.18	A
ATOM	1052	O	HIS	224	-3.338	1.732	-1.520	1.00	14.36	A
ATOM	1053	N	LEU	225	-4.970	0.673	-0.468	1.00	16.85	A
ATOM	1054	H	LEU	225	-5.317	-0.238	-0.252	1.00	15.00	A
ATOM	1055	CA	LEU	225	-5.395	1.885	0.256	1.00	15.55	A
ATOM	1056	CB	LEU	225	-6.927	2.082	0.208	1.00	17.15	A
ATOM	1057	CG	LEU	225	-7.495	2.456	-1.154	1.00	18.03	A
ATOM	1058	CD1	LEU	225	-6.792	3.659	-1.774	1.00	19.34	A
ATOM	1059	CD2	LEU	225	-8.994	2.659	-1.098	1.00	13.66	A
ATOM	1060	C	LEU	225	-5.074	1.758	1.739	1.00	14.77	A
ATOM	1061	O	LEU	225	-5.347	0.726	2.345	1.00	12.20	A
ATOM	1062	N	GLY	226	-4.544	2.829	2.344	1.00	18.04	A
ATOM	1063	H	GLY	226	-4.218	3.616	1.813	1.00	15.00	A
ATOM	1064	CA	GLY	226	-4.541	2.833	3.841	1.00	18.37	A
ATOM	1065	C	GLY	226	-4.193	4.171	4.544	1.00	17.08	A
ATOM	1066	O	GLY	226	-3.389	4.906	4.055	1.00	13.75	A
ATOM	1067	N	GLY	227	-4.781	4.457	5.725	1.00	16.30	A
ATOM	1068	H	GLY	227	-5.434	3.771	6.036	1.00	15.00	A
ATOM	1069	CA	GLY	227	-4.379	5.649	6.490	1.00	8.52	A
ATOM	1070	C	GLY	227	-4.935	5.631	7.959	1.00	12.75	A
ATOM	1071	O	GLY	227	-5.651	4.748	8.466	1.00	10.57	A
ATOM	1072	N	VAL	228	-4.588	6.698	8.675	1.00	9.23	A
ATOM	1073	H	VAL	228	-4.040	7.398	8.222	1.00	15.00	A
ATOM	1074	CA	VAL	228	-5.110	6.818	10.067	1.00	11.74	A
ATOM	1075	CB	VAL	228	-4.085	7.320	11.144	1.00	14.30	A
ATOM	1076	CG1	VAL	228	-2.830	6.445	11.333	1.00	10.73	A
ATOM	1077	CG2	VAL	228	-4.789	7.565	12.479	1.00	17.07	A
ATOM	1078	C	VAL	228	-6.238	7.803	10.098	1.00	9.03	A
ATOM	1079	O	VAL	228	-6.089	8.937	9.649	1.00	12.01	A

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ATOM	1080	N	PHE	229	-7.347	7.299	10.640	1.00	8.88	A
ATOM	1081	H	PHE	229	-7.329	6.332	10.922	1.00	15.00	A
ATOM	1082	CA	PHE	229	-8.566	8.106	10.772	1.00	11.18	A
ATOM	1083	CB	PHE	229	-9.578	7.687	9.686	1.00	8.11	A
ATOM	1084	CG	PHE	229	-9.063	7.912	8.233	1.00	8.41	A
ATOM	1085	CD1	PHE	229	-9.140	9.196	7.649	1.00	10.03	A
ATOM	1086	CD2	PHE	229	-8.433	6.883	7.517	1.00	6.57	A
ATOM	1087	CE1	PHE	229	-8.512	9.443	6.395	1.00	5.18	A
ATOM	1088	CE2	PHE	229	-7.771	7.128	6.282	1.00	4.26	A
ATOM	1089	CZ	PHE	229	-7.813	8.424	5.731	1.00	5.71	A
ATOM	1090	C	PHE	229	-9.202	8.014	12.197	1.00	14.39	A
ATOM	1091	O	PHE	229	-9.116	7.000	12.870	1.00	13.90	A
ATOM	1092	N	GLU	230	-9.863	9.064	12.672	1.00	17.93	A
ATOM	1093	H	GLU	230	-9.912	9.892	12.113	1.00	15.00	A
ATOM	1094	CA	GLU	230	-10.856	8.944	13.770	1.00	18.08	A
ATOM	1095	CB	GLU	230	-11.218	10.303	14.393	1.00	16.17	A
ATOM	1096	CG	GLU	230	-11.068	10.090	15.889	1.00	27.69	A
ATOM	1097	CD	GLU	230	-12.314	10.091	16.805	1.00	33.06	A
ATOM	1098	OE1	GLU	230	-13.355	10.707	16.552	1.00	38.26	A
ATOM	1099	OE2	GLU	230	-12.218	9.477	17.863	1.00	38.14	A
ATOM	1100	C	GLU	230	-12.225	8.268	13.453	1.00	18.70	A
ATOM	1101	O	GLU	230	-12.967	8.519	12.492	1.00	21.58	A
ATOM	1102	N	LEU	231	-12.542	7.334	14.361	1.00	13.79	A
ATOM	1103	H	LEU	231	-11.840	7.125	15.015	1.00	15.00	A
ATOM	1104	CA	LEU	231	-13.885	6.836	14.330	1.00	13.52	A
ATOM	1105	CB	LEU	231	-13.954	5.378	14.002	1.00	13.90	A
ATOM	1106	CG	LEU	231	-13.199	5.064	12.725	1.00	15.44	A
ATOM	1107	CD1	LEU	231	-13.781	5.712	11.436	1.00	10.24	A
ATOM	1108	CD2	LEU	231	-12.970	3.569	12.769	1.00	11.74	A
ATOM	1109	C	LEU	231	-14.638	7.074	15.591	1.00	14.88	A
ATOM	1110	O	LEU	231	-14.145	6.912	16.692	1.00	12.46	A
ATOM	1111	N	GLN	232	-15.891	7.411	15.350	1.00	19.40	A
ATOM	1112	H	GLN	232	-16.107	7.560	14.394	1.00	15.00	A
ATOM	1113	CA	GLN	232	-16.920	7.509	16.389	1.00	21.07	A
ATOM	1114	CB	GLN	232	-18.132	8.234	15.804	1.00	23.55	A
ATOM	1115	CG	GLN	232	-17.792	9.709	15.687	1.00	28.60	A
ATOM	1116	CD	GLN	232	-17.625	10.200	17.102	1.00	33.66	A
ATOM	1117	OE1	GLN	232	-18.623	10.472	17.742	1.00	38.08	A
ATOM	1118	NE2	GLN	232	-16.380	10.254	17.596	1.00	33.41	A
ATOM	1119	HE21	GLN	232	-15.596	10.186	16.972	1.00	15.00	A
ATOM	1120	HE22	GLN	232	-16.387	10.470	18.576	1.00	15.00	A
ATOM	1121	C	GLN	232	-17.402	6.148	16.851	1.00	21.86	A
ATOM	1122	O	GLN	232	-17.368	5.218	16.052	1.00	21.58	A
ATOM	1123	N	PRO	233	-17.906	6.013	18.115	1.00	22.31	A
ATOM	1124	CD	PRO	233	-17.962	7.033	19.168	1.00	21.41	A
ATOM	1125	CA	PRO	233	-18.570	4.747	18.442	1.00	21.21	A
ATOM	1126	CB	PRO	233	-19.013	4.987	19.866	1.00	23.88	A
ATOM	1127	CG	PRO	233	-18.661	6.404	20.339	1.00	20.95	A
ATOM	1128	C	PRO	233	-19.667	4.417	17.434	1.00	23.66	A
ATOM	1129	O	PRO	233	-20.275	5.319	16.875	1.00	26.89	A
ATOM	1130	N	GLY	234	-19.731	3.140	17.059	1.00	22.77	A
ATOM	1131	H	GLY	234	-19.082	2.466	17.417	1.00	15.00	A
ATOM	1132	CA	GLY	234	-20.766	2.767	16.072	1.00	19.45	A
ATOM	1133	C	GLY	234	-20.545	3.241	14.625	1.00	19.67	A
ATOM	1134	O	GLY	234	-21.299	2.980	13.715	1.00	23.81	A
ATOM	1135	N	ALA	235	-19.405	3.926	14.368	1.00	18.89	A
ATOM	1136	H	ALA	235	-19.096	4.485	15.135	1.00	15.00	A
ATOM	1137	CA	ALA	235	-18.431	3.515	13.296	1.00	22.17	A
ATOM	1138	CB	ALA	235	-18.193	2.042	13.039	1.00	6.68	A
ATOM	1139	C	ALA	235	-18.540	4.160	11.993	1.00	21.96	A

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ATOM	1143	C	ALA	235	-18.486	5.388	10.101	1.00	16.42	A
ATOM	1144	N	SER	236	-18.699	3.498	10.787	1.00	21.84	A
ATOM	1145	H	SER	236	-18.824	4.326	10.254	1.00	15.00	A
ATOM	1146	CA	SER	236	-18.630	2.227	9.961	1.00	17.61	A
ATOM	1147	CB	SER	236	-19.905	1.876	9.160	1.00	14.96	A
ATOM	1148	OG	SER	236	-20.662	0.908	9.533	1.00	21.05	A
ATOM	1149	HG	SER	236	-21.599	0.910	9.647	1.00	15.00	A
ATOM	1150	C	SER	236	-17.794	2.538	8.714	1.00	13.65	A
ATOM	1151	O	SER	236	-17.939	3.614	8.131	1.00	16.29	A
ATOM	1152	N	VAL	237	-16.986	1.567	8.286	1.00	14.95	A
ATOM	1153	H	VAL	237	-16.764	0.823	8.949	1.00	15.00	A
ATOM	1154	CA	VAL	237	-16.201	1.802	7.077	1.00	11.42	A
ATOM	1155	CB	VAL	237	-14.681	2.004	7.284	1.00	12.49	A
ATOM	1156	CG1	VAL	237	-14.113	0.726	7.939	1.00	13.10	A
ATOM	1157	CG2	VAL	237	-14.254	3.396	7.846	1.00	10.27	A
ATOM	1158	C	VAL	237	-16.468	0.746	6.035	1.00	8.76	A
ATOM	1159	O	VAL	237	-16.827	-0.363	6.341	1.00	12.84	A
ATOM	1160	N	PHE	238	-16.354	1.158	4.773	1.00	12.45	A
ATOM	1161	H	PHE	238	-16.139	2.128	4.652	1.00	15.00	A
ATOM	1162	CA	PHE	238	-16.521	0.213	3.653	1.00	11.21	A
ATOM	1163	CB	PHE	238	-18.013	0.137	3.322	1.00	13.00	A
ATOM	1164	CG	PHE	238	-18.634	1.466	2.899	1.00	12.17	A
ATOM	1165	CD1	PHE	238	-18.763	1.812	1.518	1.00	12.94	A
ATOM	1166	CD2	PHE	238	-19.135	2.332	3.887	1.00	10.55	A
ATOM	1167	CE1	PHE	238	-19.407	3.010	1.092	1.00	14.01	A
ATOM	1168	CE2	PHE	238	-19.786	3.504	3.470	1.00	12.74	A
ATOM	1169	CZ	PHE	238	-19.917	3.836	2.100	1.00	13.17	A
ATOM	1170	C	PHE	238	-15.725	0.582	2.379	1.00	11.20	A
ATOM	1171	O	PHE	238	-15.137	1.638	2.267	1.00	8.73	A
ATOM	1172	N	VAL	239	-15.726	-0.300	1.383	1.00	14.34	A
ATOM	1173	H	VAL	239	-16.187	-1.170	1.523	1.00	15.00	A
ATOM	1174	CA	VAL	239	-14.982	0.027	0.154	1.00	14.65	A
ATOM	1175	CB	VAL	239	-13.900	-1.043	-0.162	1.00	14.09	A
ATOM	1176	CG1	VAL	239	-13.004	-1.318	1.038	1.00	14.55	A
ATOM	1177	CG2	VAL	239	-13.064	-0.594	-1.361	1.00	14.74	A
ATOM	1178	C	VAL	239	-15.930	0.081	-1.043	1.00	18.32	A
ATOM	1179	O	VAL	239	-16.558	-0.903	-1.369	1.00	18.99	A
ATOM	1180	N	ASN	240	-16.000	1.207	-1.707	1.00	19.26	A
ATOM	1181	H	ASN	240	-15.420	1.947	-1.383	1.00	15.00	A
ATOM	1182	CA	ASN	240	-16.613	1.355	-3.031	1.00	21.66	A
ATOM	1183	CB	ASN	240	-16.850	2.856	-3.095	1.00	24.58	A
ATOM	1184	CG	ASN	240	-18.167	3.077	-3.708	1.00	29.09	A
ATOM	1185	OD1	ASN	240	-18.948	2.123	-3.740	1.00	35.44	A
ATOM	1186	ND2	ASN	240	-18.293	4.331	-4.166	1.00	34.71	A
ATOM	1187	HD21	ASN	240	-19.149	4.489	-4.657	1.00	15.00	A
ATOM	1188	C	ASN	240	-15.669	0.950	-4.184	1.00	20.96	A
ATOM	1189	O	ASN	240	-14.473	1.128	-4.058	1.00	20.99	A
ATOM	1190	N	VAL	241	-16.189	0.383	-5.275	1.00	21.52	A
ATOM	1191	H	VAL	241	-17.182	0.230	-5.295	1.00	15.00	A
ATOM	1192	CA	VAL	241	-15.387	0.439	-6.516	1.00	20.56	A
ATOM	1193	CB	VAL	241	-14.581	-0.850	-6.849	1.00	18.02	A
ATOM	1194	CG1	VAL	241	-15.501	-2.058	-7.063	1.00	15.06	A
ATOM	1195	CG2	VAL	241	-13.597	-1.259	-5.764	1.00	20.05	A
ATOM	1196	C	VAL	241	-16.253	0.758	-7.741	1.00	18.88	A
ATOM	1197	O	VAL	241	-17.441	0.500	-7.819	1.00	18.63	A
ATOM	1198	N	THR	242	-15.541	1.162	-8.762	1.00	21.24	A
ATOM	1199	H	THR	242	-14.704	1.653	-8.486	1.00	15.00	A
ATOM	1200	CA	THR	242	-16.246	1.476	-10.031	1.00	20.63	A
ATOM	1201	CB	THR	242	-15.342	2.269	-10.981	1.00	15.80	A
ATOM	1202	OG1	THR	242	-14.035	1.663	-10.953	1.00	17.72	A

FIGURE 1U

ATOM	1230	HG1	THR	242	-13.721	1.969	-11.812	1.00	15.00	A
ATOM	1231	CG2	THR	242	-15.238	3.732	-10.651	1.00	18.04	A
ATOM	1232	C	THR	242	-16.755	0.240	-10.783	1.00	19.91	A
ATOM	1233	O	THR	242	-17.846	0.199	-11.297	1.00	21.04	A
ATOM	1234	N	ASP	243	-15.823	-0.806	-10.718	1.00	21.98	A
ATOM	1235	H	ASP	243	-15.087	-0.580	-10.221	1.00	15.00	A
ATOM	1236	CA	ASP	243	-16.092	-1.977	-11.628	1.00	21.26	A
ATOM	1237	CB	ASP	243	-14.905	-2.126	-12.594	1.00	22.05	A
ATOM	1238	CG	ASP	243	-14.932	-0.954	-13.492	1.00	26.23	A
ATOM	1239	OD1	ASP	243	-14.314	0.051	-13.115	1.00	26.43	A
ATOM	1240	OD2	ASP	243	-15.588	-1.033	-14.535	1.00	33.00	A
ATOM	1241	C	ASP	243	-16.123	-3.308	-10.923	1.00	20.36	A
ATOM	1242	O	ASP	243	-15.148	-4.072	-10.967	1.00	20.43	A
ATOM	1243	N	PRO	244	-17.204	-3.553	-10.154	1.00	19.92	A
ATOM	1244	CD	PRO	244	-18.481	-2.871	-10.071	1.00	16.83	A
ATOM	1245	CA	PRO	244	-17.120	-4.706	-9.269	1.00	19.13	A
ATOM	1246	CB	PRO	244	-18.293	-4.535	-8.275	1.00	15.33	A
ATOM	1247	CG	PRO	244	-18.890	-3.174	-8.634	1.00	15.21	A
ATOM	1248	C	PRO	244	-16.975	-6.034	-9.974	1.00	19.29	A
ATOM	1249	O	PRO	244	-16.194	-6.859	-9.548	1.00	23.48	A
ATOM	1250	N	SER	245	-17.581	-6.163	-11.150	1.00	22.60	A
ATOM	1251	H	SER	245	-18.220	-5.459	-11.473	1.00	15.00	A
ATOM	1252	CA	SER	245	-17.414	-7.429	-11.942	1.00	25.50	A
ATOM	1253	CB	SER	245	-18.256	-7.369	-13.234	1.00	21.36	A
ATOM	1254	OG	SER	245	-19.667	-7.567	-12.981	1.00	38.26	A
ATOM	1255	HG	SER	245	-19.848	-7.390	-12.038	1.00	15.00	A
ATOM	1256	C	SER	245	-15.955	-7.776	-12.328	1.00	24.14	A
ATOM	1257	O	SER	245	-15.477	-8.859	-12.623	1.00	24.84	A
ATOM	1258	N	GLN	246	-15.177	-6.689	-12.385	1.00	28.52	A
ATOM	1259	H	GLN	246	-15.638	-5.804	-12.265	1.00	15.00	A
ATOM	1260	CA	GLN	246	-13.743	-6.923	-12.590	1.00	26.45	A
ATOM	1261	CB	GLN	246	-13.144	-5.645	-13.233	1.00	29.90	A
ATOM	1262	CG	GLN	246	-13.403	-5.435	-14.758	1.00	26.84	A
ATOM	1263	CD	GLN	246	-14.862	-5.341	-15.129	1.00	21.60	A
ATOM	1264	OE1	GLN	246	-15.538	-4.503	-14.616	1.00	24.20	A
ATOM	1265	NE2	GLN	246	-15.334	-6.234	-15.975	1.00	26.15	A
ATOM	1266	HE21	GLN	246	-14.763	-6.924	-16.423	1.00	15.00	A
ATOM	1267	HE22	GLN	246	-16.320	-6.119	-16.084	1.00	15.00	A
ATOM	1268	C	GLN	246	-12.936	-7.372	-11.363	1.00	27.14	A
ATOM	1269	O	GLN	246	-11.721	-7.570	-11.454	1.00	25.73	A
ATOM	1270	N	VAL	247	-13.615	-7.395	-10.196	1.00	23.70	A
ATOM	1271	H	VAL	247	-14.600	-7.594	-10.146	1.00	15.00	A
ATOM	1272	CA	VAL	247	-12.728	-7.569	-9.097	1.00	21.91	A
ATOM	1273	CB	VAL	247	-13.156	-6.814	-7.859	1.00	21.59	A
ATOM	1274	CG1	VAL	247	-14.027	-7.616	-6.962	1.00	24.52	A
ATOM	1275	CG2	VAL	247	-13.680	-5.409	-8.167	1.00	21.61	A
ATOM	1276	C	VAL	247	-12.258	-8.998	-8.910	1.00	21.55	A
ATOM	1277	O	VAL	247	-12.946	-9.912	-9.251	1.00	19.53	A
ATOM	1278	N	SER	248	-11.000	-9.152	-8.444	1.00	21.31	A
ATOM	1279	H	SER	248	-10.556	-8.342	-8.070	1.00	15.00	A
ATOM	1280	CA	SER	248	-10.414	-10.499	-8.327	1.00	21.97	A
ATOM	1281	CB	SER	248	-8.939	-10.571	-8.828	1.00	23.61	A
ATOM	1282	OG	SER	248	-8.860	-9.952	-10.128	1.00	20.21	A
ATOM	1283	HG	SER	248	-9.752	-10.027	-10.496	1.00	15.00	A
ATOM	1284	C	SER	248	-10.538	-11.076	-6.946	1.00	19.28	A
ATOM	1285	O	SER	248	-10.048	-10.409	-6.052	1.00	20.64	A
ATOM	1286	N	HIS	249	-11.269	-12.204	-6.814	1.00	18.72	A
ATOM	1287	H	HIS	249	-11.284	-12.753	-7.674	1.00	15.00	A
ATOM	1288	CA	HIS	249	-11.640	-12.673	-5.478	1.00	17.22	A
ATOM	1289	CB	HIS	249	-13.090	-13.152	-5.484	1.00	13.10	A

FIGURE 1V

ATOM	1260	CG	HIS	249	-13.919	-11.905	-5.551	1.00	10.13	A
ATOM	1261	ND1	HIS	249	-14.137	-11.129	-4.486	1.00	13.47	A
ATOM	1262	HD1	HIS	249	-13.720	-11.294	-3.611	1.00	18.00	A
ATOM	1263	CD2	HIS	249	-14.662	-11.414	-6.610	1.00	11.62	A
ATOM	1264	NE2	HIS	249	-15.317	-10.347	-6.134	1.00	15.81	A
ATOM	1265	CE1	HIS	249	-15.028	-10.142	-4.821	1.00	12.36	A
ATOM	1266	C	HIS	249	-10.701	-13.683	-4.858	1.00	23.88	A
ATOM	1267	O	HIS	249	-11.103	-14.729	-4.359	1.00	21.98	A
ATOM	1268	N	GLY	250	-9.398	-13.258	-4.878	1.00	29.10	A
ATOM	1269	H	GLY	250	-9.252	-12.351	-5.253	1.00	15.00	A
ATOM	1270	CA	GLY	250	-8.410	-14.041	-4.115	1.00	24.27	A
ATOM	1271	C	GLY	250	-8.336	-15.372	-4.743	1.00	25.93	A
ATOM	1272	O	GLY	250	-8.940	-15.520	-5.795	1.00	29.26	A
ATOM	1273	N	THR	251	-7.594	-16.302	-4.127	1.00	22.38	A
ATOM	1274	H	THR	251	-7.485	-17.038	-4.804	1.00	15.00	A
ATOM	1275	CA	THR	251	-7.111	-16.139	-2.725	1.00	21.12	A
ATOM	1276	CB	THR	251	-6.988	-17.525	-1.933	1.00	24.76	A
ATOM	1277	OG1	THR	251	-5.877	-17.641	-0.981	1.00	22.90	A
ATOM	1278	HG1	THR	251	-6.063	-18.366	-0.381	1.00	15.00	A
ATOM	1279	CG2	THR	251	-6.968	-18.722	-2.890	1.00	22.77	A
ATOM	1280	C	THR	251	-5.952	-15.158	-2.473	1.00	17.96	A
ATOM	1281	O	THR	251	-4.969	-15.043	-3.213	1.00	12.30	A
ATOM	1282	N	GLY	252	-6.241	-14.367	-1.419	1.00	16.85	A
ATOM	1283	H	GLY	252	-7.093	-14.432	-0.862	1.00	15.00	A
ATOM	1284	CA	GLY	252	-5.277	-13.375	-0.928	1.00	13.16	A
ATOM	1285	C	GLY	252	-5.357	-12.058	-1.670	1.00	15.51	A
ATOM	1286	O	GLY	252	-4.580	-11.168	-1.439	1.00	15.18	A
ATOM	1287	N	PHE	253	-6.189	-12.063	-2.744	1.00	16.66	A
ATOM	1288	H	PHE	253	-6.868	-12.805	-2.761	1.00	15.00	A
ATOM	1289	CA	PHE	253	-6.110	-10.892	-3.651	1.00	15.77	A
ATOM	1290	CB	PHE	253	-6.649	-11.216	-5.100	1.00	17.11	A
ATOM	1291	CG	PHE	253	-5.595	-11.840	-5.994	1.00	11.82	A
ATOM	1292	CD1	PHE	253	-4.385	-11.175	-6.231	1.00	13.69	A
ATOM	1293	CD2	PHE	253	-5.845	-13.089	-6.558	1.00	18.59	A
ATOM	1294	CE1	PHE	253	-3.364	-11.771	-6.993	1.00	14.39	A
ATOM	1295	CE2	PHE	253	-4.840	-13.680	-7.363	1.00	21.37	A
ATOM	1296	CZ	PHE	253	-3.612	-13.014	-7.562	1.00	15.72	A
ATOM	1297	C	PHE	253	-6.740	-9.599	-3.147	1.00	13.88	A
ATOM	1298	O	PHE	253	-6.347	-8.477	-3.453	1.00	14.27	A
ATOM	1299	N	THR	254	-7.865	-9.837	-2.502	1.00	14.00	A
ATOM	1300	H	THR	254	-8.079	-10.748	-2.124	1.00	15.00	A
ATOM	1301	CA	THR	254	-8.741	-8.681	-2.185	1.00	14.09	A
ATOM	1302	CB	THR	254	-9.908	-8.469	-3.201	1.00	11.66	A
ATOM	1303	OG1	THR	254	-9.414	-8.325	-4.536	1.00	13.08	A
ATOM	1304	HG1	THR	254	-9.826	-9.054	-4.992	1.00	15.00	A
ATOM	1305	CG2	THR	254	-10.882	-7.321	-2.885	1.00	13.78	A
ATOM	1306	C	THR	254	-9.270	-8.779	-0.738	1.00	12.36	A
ATOM	1307	O	THR	254	-9.906	-9.695	-0.240	1.00	14.54	A
ATOM	1308	N	SER	255	-9.007	-7.683	-0.027	1.00	13.42	A
ATOM	1309	H	SER	255	-8.425	-7.021	-0.490	1.00	15.00	A
ATOM	1310	CA	SER	255	-9.032	-7.725	1.431	1.00	7.59	A
ATOM	1311	CB	SER	255	-7.793	-8.466	1.976	1.00	6.39	A
ATOM	1312	OG	SER	255	-6.704	-7.560	2.041	1.00	9.69	A
ATOM	1313	HG	SER	255	-5.920	-8.031	1.741	1.00	15.00	A
ATOM	1314	C	SER	255	-9.248	-6.341	2.085	1.00	10.05	A
ATOM	1315	O	SER	255	-9.191	-5.254	1.492	1.00	15.21	A
ATOM	1316	N	PHE	256	-9.653	-6.385	3.369	1.00	8.54	A
ATOM	1317	H	PHE	256	-9.700	-7.323	3.733	1.00	15.00	A
ATOM	1318	CA	PHE	256	-10.114	-5.168	4.035	1.00	7.94	A
ATOM	1319	CB	PHE	256	-11.605	-5.009	3.679	1.00	11.65	A

FIGURE 1W

ATOM	1321	CG	PHE	255	-12.376	-3.824	4.238	1.00	8.70	A
ATOM	1322	CD1	PHE	255	-11.766	-2.870	4.533	1.00	11.20	A
ATOM	1323	CD2	PHE	255	-13.756	-3.976	4.327	1.00	8.12	A
ATOM	1324	CE1	PHE	255	-12.503	-1.490	5.034	1.00	11.49	A
ATOM	1325	CE2	PHE	255	-14.514	-2.849	4.734	1.00	8.86	A
ATOM	1326	CZ	PHE	255	-13.862	-1.657	5.211	1.00	9.27	A
ATOM	1327	C	PHE	255	-9.933	-5.268	5.560	1.00	11.92	A
ATOM	1328	O	PHE	255	-10.195	-6.290	6.177	1.00	9.43	A
ATOM	1329	N	GLY	256	-9.420	-4.207	6.169	1.00	10.57	A
ATOM	1330	H	GLY	256	-9.217	-3.365	5.653	1.00	15.00	A
ATOM	1331	CA	GLY	256	-9.368	-4.406	7.612	1.00	11.26	A
ATOM	1332	C	GLY	256	-8.965	-3.122	8.287	1.00	11.14	A
ATOM	1333	O	GLY	256	-8.916	-2.068	7.679	1.00	10.81	A
ATOM	1334	N	LEU	257	-8.688	-3.277	9.565	1.00	12.61	A
ATOM	1335	H	LEU	257	-8.776	-4.204	9.943	1.00	15.00	A
ATOM	1336	CA	LEU	257	-8.434	-2.098	10.426	1.00	14.72	A
ATOM	1337	CB	LEU	257	-9.751	-1.212	10.704	1.00	14.67	A
ATOM	1338	CG	LEU	257	-10.991	-1.863	11.379	1.00	18.02	A
ATOM	1339	CD1	LEU	257	-12.317	-1.125	11.094	1.00	15.05	A
ATOM	1340	CD2	LEU	257	-10.743	-2.047	12.905	1.00	15.42	A
ATOM	1341	C	LEU	257	-7.737	-2.525	11.709	1.00	11.84	A
ATOM	1342	O	LEU	257	-7.851	-3.690	12.096	1.00	7.91	A
ATOM	1343	N	LEU	258	-7.058	-1.537	12.343	1.00	11.64	A
ATOM	1344	H	LEU	258	-6.883	-0.685	11.844	1.00	15.00	A
ATOM	1345	CA	LEU	258	-6.581	-1.780	13.714	1.00	9.53	A
ATOM	1346	CB	LEU	258	-5.155	-2.417	13.831	1.00	7.40	A
ATOM	1347	CG	LEU	258	-4.194	-1.621	12.931	1.00	11.40	A
ATOM	1348	CD1	LEU	258	-3.355	-2.412	11.926	1.00	7.83	A
ATOM	1349	CD2	LEU	258	-3.379	-0.670	13.808	1.00	13.30	A
ATOM	1350	C	LEU	258	-6.652	-0.497	14.531	1.00	10.40	A
ATOM	1351	O	LEU	258	-6.202	0.556	14.082	1.00	9.73	A
ATOM	1352	N	LYS	259	-7.193	-0.629	15.762	1.00	12.00	A
ATOM	1353	H	LYS	259	-7.395	-1.553	16.115	1.00	15.00	A
ATOM	1354	CA	LYS	259	-7.069	0.521	16.693	1.00	13.51	A
ATOM	1355	CB	LYS	259	-8.014	0.312	17.885	1.00	13.49	A
ATOM	1356	CG	LYS	259	-8.378	1.656	18.521	1.00	17.16	A
ATOM	1357	CD	LYS	259	-9.435	1.456	19.596	1.00	12.01	A
ATOM	1358	CE	LYS	259	-10.151	2.681	20.121	1.00	11.41	A
ATOM	1359	NZ	LYS	259	-9.175	3.595	20.697	1.00	13.33	A
ATOM	1360	HZ1	LYS	259	-8.534	3.932	19.954	1.00	15.00	A
ATOM	1361	HZ2	LYS	259	-9.693	4.404	21.095	1.00	15.00	A
ATOM	1362	HZ3	LYS	259	-8.638	3.136	21.458	1.00	15.00	A
ATOM	1363	C	LYS	259	-5.648	0.921	17.125	1.00	16.54	A
ATOM	1364	O	LYS	259	-4.828	0.112	17.481	1.00	15.61	A
ATOM	1365	N	LEU	260	-5.353	2.199	17.015	1.00	14.78	A
ATOM	1366	H	LEU	260	-6.089	2.838	16.856	1.00	15.00	A
ATOM	1367	CB	LEU	260	-3.705	4.005	17.185	1.00	19.53	A
ATOM	1368	CG	LEU	260	-3.177	4.309	15.787	1.00	16.82	A
ATOM	1369	CD1	LEU	260	-3.010	5.779	15.767	1.00	12.45	A
ATOM	1370	CD2	LEU	260	-4.010	3.906	14.577	1.00	18.20	A
ATOM	1371	C	LEU	260	-4.243	2.667	19.225	1.00	20.80	A
ATOM	1372	OXT1	LEU	260	-5.363	2.741	19.746	1.00	22.59	A
ATOM	1373	OXT2	LEU	260	-3.221	2.696	19.913	1.00	26.97	A
ATOM	1374	CA	LEU	260	-4.122	2.604	17.684	1.00	18.13	A
ATOM	1375	O	HOH	501	-20.040	9.837	7.596	1.00	16.33	W
ATOM	1376	H1	HOH	501	-19.411	10.547	7.803	1.00	10.00	W
ATOM	1377	H2	HOH	501	-19.615	9.317	6.900	1.00	10.00	W
ATOM	1378	O	HOH	502	-9.727	11.545	10.743	1.00	10.94	W
ATOM	1379	H1	HOH	502	-10.039	11.934	9.919	1.00	15.00	W
ATOM	1380	H2	HOH	502	-10.233	12.125	11.315	1.00	15.00	W

FIGURE 1X

ATOM	1380	O	HOH	503	-8.158	13.188	13.681	1.00	30.64	W
ATOM	1381	H1	HOH	503	-8.715	12.529	13.2[illegible]	1.00	15.00	W
ATOM	1382	H2	HOH	503	-8.700	13.944	13.574	1.00	15.00	W
ATOM	1383	O	HOH	504	-16.772	8.440	12.789	1.00	10.00	W
ATOM	1384	H1	HOH	504	-17.194	9.259	12.886	1.00	10.00	W
ATOM	1385	H2	HOH	504	-15.921	8.763	12.582	1.00	10.00	W
ATOM	1386	O	HOH	505	-25.173	7.297	7.925	1.00	47.03	W
ATOM	1387	H1	HOH	505	-24.690	8.064	8.239	1.00	10.00	W
ATOM	1388	H2	HOH	505	-25.990	7.684	7.583	1.00	10.00	W
ATOM	1389	O	HOH	506	-23.612	14.948	13.859	1.00	36.14	W
ATOM	1390	H1	HOH	506	-24.160	15.702	13.605	1.00	10.00	W
ATOM	1391	H2	HOH	506	-23.282	15.191	14.748	1.00	10.00	W
ATOM	1392	O	HOH	507	-17.329	-8.460	-7.186	1.00	34.02	W
ATOM	1393	O	HOH	508	-18.687	-7.253	-3.843	1.00	63.14	W
ATOM	1394	O	HOH	509	-7.157	11.327	3.239	1.00	22.26	W
ATOM	1395	O	HOH	510	-19.322	7.486	-2.227	1.00	37.69	W
ATOM	1396	O	HOH	511	-14.645	-7.711	-1.931	1.00	26.48	W
ATOM	1397	O	HOH	512	-18.377	-9.754	12.556	1.00	24.86	W
ATOM	1398	O	HOH	513	0.030	0.048	-13.455	1.00	26.05	W
ATOM	1399	O	HOH	514	-8.938	5.945	22.862	1.00	34.39	W
ATOM	1400	O	HOH	515	-29.446	-4.922	-7.247	1.00	41.61	W
ATOM	1401	O	HOH	516	-12.982	10.220	10.038	1.00	47.16	W
ATOM	1402	O	HOH	517	-21.797	-9.377	7.242	1.00	60.65	W
ATOM	1403	O	HOH	518	-7.867	8.165	19.484	1.00	40.46	W
ATOM	1404	O	HOH	520	-15.588	-14.701	14.628	1.00	63.80	W
ATOM	1405	O	HOH	521	-21.844	7.778	20.415	1.00	35.72	W
ATOM	1406	O	HOH	522	-6.555	-3.308	-15.790	1.00	33.63	W
ATOM	1407	O	HOH	523	-9.046	-13.476	-8.051	1.00	44.08	W
ATOM	1408	O	HOH	524	-17.413	-9.311	17.071	1.00	34.06	W
ATOM	1409	O	HOH	525	-23.838	4.781	19.884	1.00	37.99	W
ATOM	1410	O	HOH	526	-26.323	15.525	10.379	1.00	72.49	W
ATOM	1411	O	HOH	527	-3.167	-13.749	-10.820	1.00	43.99	W
ATOM	1412	O	HOH	528	-0.470	2.513	17.943	1.00	63.68	W
ATOM	1413	O	HOH	529	-5.580	-12.778	-14.864	1.00	47.52	W
ATOM	1414	O	HOH	530	-2.641	7.004	2.495	1.00	18.07	W
ATOM	1415	O	HOH	531	-6.472	12.847	0.156	1.00	24.96	W
ATOM	1416	O	HOH	532	-10.363	-16.426	-0.360	1.00	63.56	W
ATOM	1417	O	HOH	533	-1.378	-17.183	-13.053	1.00	67.67	W
ATOM	1418	O	HOH	534	-4.774	9.073	-0.651	1.00	23.36	W
ATOM	1419	O	HOH	535	-18.917	-13.857	6.913	1.00	32.28	W
ATOM	1420	O	HOH	536	-23.062	3.270	0.454	1.00	52.03	W
ATOM	1421	O	HOH	537	-25.906	9.022	16.986	1.00	44.75	W
ATOM	1422	O	HOH	538	-21.729	16.972	17.027	1.00	53.12	W
ATOM	1423	O	HOH	539	-9.084	11.806	17.034	1.00	70.90	W
ATOM	1424	O	HOH	540	-10.938	-13.296	15.207	1.00	35.65	W
ATOM	1425	O	HOH	541	-6.068	13.255	17.989	1.00	67.36	W
ATOM	1426	O	HOH	542	-20.593	-11.039	-9.003	1.00	96.30	W
ATOM	1427	O	HOH	543	-15.926	13.397	1.269	1.00	35.72	W
ATOM	1428	O	HOH	544	-24.591	-7.285	-2.353	1.00	43.42	W
ATOM	1429	O	HOH	545	-25.859	-2.666	-15.747	1.00	53.56	W
ATOM	1430	O	HOH	546	-23.074	-1.533	11.026	1.00	56.44	W
ATOM	1431	O	HOH	548	-8.941	-12.649	-12.394	1.00	64.34	W
ATOM	1432	O	HOH	549	-14.150	6.038	-12.250	1.00	41.38	W
ATOM	1433	O	HOH	550	-14.274	-0.613	18.441	1.00	56.17	W
ATOM	1434	O	HOH	551	-12.241	-19.609	8.637	1.00	80.90	W
ATOM	1435	O	HOH	552	-10.316	15.578	10.166	1.00	39.58	W
ATOM	1436	O	HOH	553	-15.367	10.941	14.659	1.00	40.40	W
ATOM	1437	O	HOH	554	-2.322	1.830	-5.294	1.00	33.65	W
ATOM	1438	O	HOH	555	-22.393	-14.875	-4.217	1.00	52.40	W
ATOM	1439	O	HOH	556	-22.120	14.279	7.189	1.00	38.55	W

FIGURE 1Y

```
ATOM   1440  O   HOH   557     -28.833   6.135   9.560  1.00 37.40      WW
ATOM   1441  O   HOH   558      -5.854 -16.509  13.292  1.00 88.88      WW
ATOM   1442  O   HOH   559     -22.996  12.522   1.162  1.00 60.77      WW
ATOM   1443  O   HOH   560     -13.764   2.268 -14.743  1.00 27.47      WW
ATOM   1444  O   HOH   561     -15.556   7.750  -5.628  1.00 75.88      WW
ATOM   1445  O   HOH   562      -1.970 -15.363 -17.719  1.00 76.30      WW
ATOM   1446  O   HOH   563     -18.939  -0.335 -13.842  1.00 48.39      WW
ATOM   1447  O   HOH   564     -12.619  14.760  -6.974  1.00100.59      WW
ATOM   1448  O   HOH   565      -9.491  18.046  13.682  1.00 87.45      WW
ATOM   1449  O   HOH   566     -11.655 -11.140  22.481  1.00 28.88      WW
ATOM   1450  O   HOH   567     -24.072  -3.264  -0.332  1.00 35.13      WW
ATOM   1451  O   HOH   568     -27.455   0.119  -7.117  1.00 71.07      WW
ATOM   1452  O   HOH   569     -14.604   3.516  -6.119  1.00 59.45      WW
ATOM   1453  O   HOH   570      -2.635  -9.566 -16.973  1.00 59.09      WW
ATOM   1454  O   HOH   571     -18.841   4.066  -7.543  1.00 34.19      WW
ATOM   1455  O   HOH   572     -24.996   1.301  17.953  1.00 70.45      WW
ATOM   1456  O   HOH   573     -14.666  16.471   8.995  1.00 62.77      WW
ATOM   1457  O   HOH   574     -14.786   1.426  10.949  1.00 82.68      WW
ATOM   1458  O   HOH   575     -16.584 -14.717  -4.352  1.00 29.09      WW
ATOM   1459  O   HOH   576     -16.273  -4.590   6.109  1.00104.64      WW
ATOM   1460  O   HOH   577     -25.471  -0.127  -2.510  1.00 62.74      WW
ATOM   1461  O   HOH   578      -7.334 -17.173  19.514  1.00 89.62      WW
ATOM   1462  O   HOH   579     -21.060  14.259  19.996  1.00 69.59      WW
ATOM   1463  O   HOH   580     -19.286   4.057 -12.816  1.00 60.37      WW
ATOM   1464  O   HOH   581     -22.445 -15.840   0.317  1.00 58.24      WW
ATOM   1465  O   HOH   582     -22.434 -10.539  12.489  1.00 70.25      WW
ATOM   1466  O   HOH   583     -21.327   3.668  -2.500  1.00 39.32      WW
ATOM   1467  O   HOH   584     -25.325   5.247  16.919  1.00 41.31      WW
ATOM   1468  O   HOH   585     -24.945 -10.718  -2.375  1.00 38.85      WW
ATOM   1469  O   HOH   586     -24.342 -13.003   1.927  1.00 70.58      WW
ATOM   1470  O   HOH   587     -18.020  11.871  11.358  1.00 64.47      WW
ATOM   1471  O   HOH   588     -27.135   6.965  13.151  1.00 53.96      WW
ATOM   1472  O   HOH   589     -14.982 -16.230  -2.494  1.00 30.24      WW
ATOM   1473  O   HOH   590      -5.646  14.418  -2.232  1.00 41.78      WW
ATOM   1474  O   HOH   591      -2.745  -0.153 -17.104  1.00 55.19      WW
ATOM   1475  O   HOH   592      -3.397  -7.012  22.477  1.00 59.46      WW
ATOM   1476  O   HOH   593     -32.916  -4.705  -4.143  1.00 51.88      WW
ATOM   1477  O   HOH   594     -10.913 -18.855  -3.503  1.00 42.29      WW
ATOM   1478  O   HOH   595     -24.157   1.821  -6.165  1.00 47.43      WW
END
```

FIGURE 2C

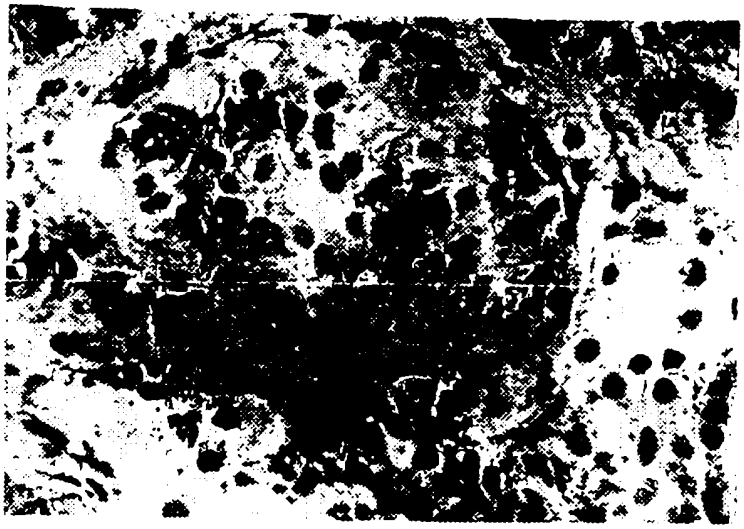

FIGURE 2B

FIGURE 2A

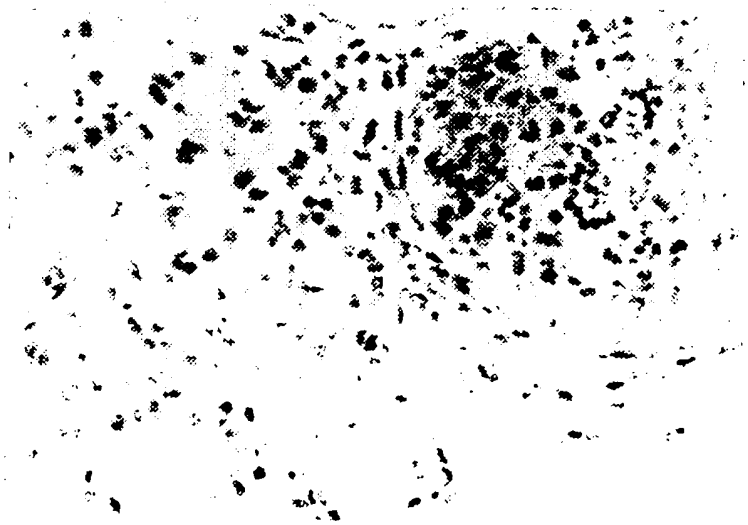

FIGURE 3C

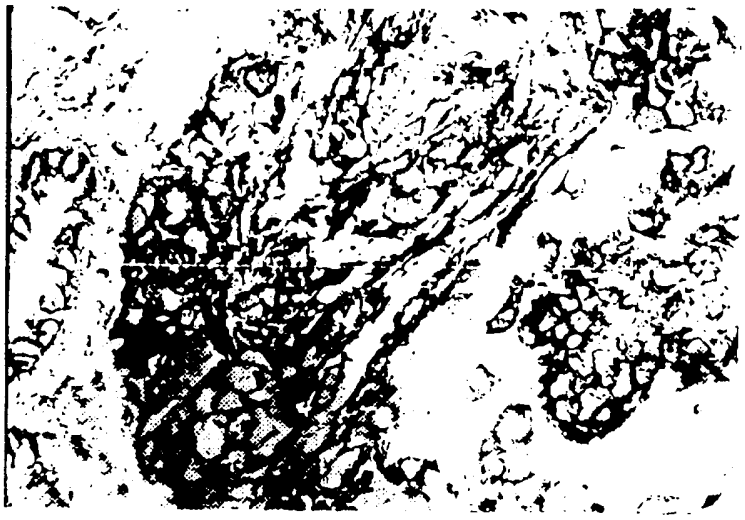

FIGURE 3B

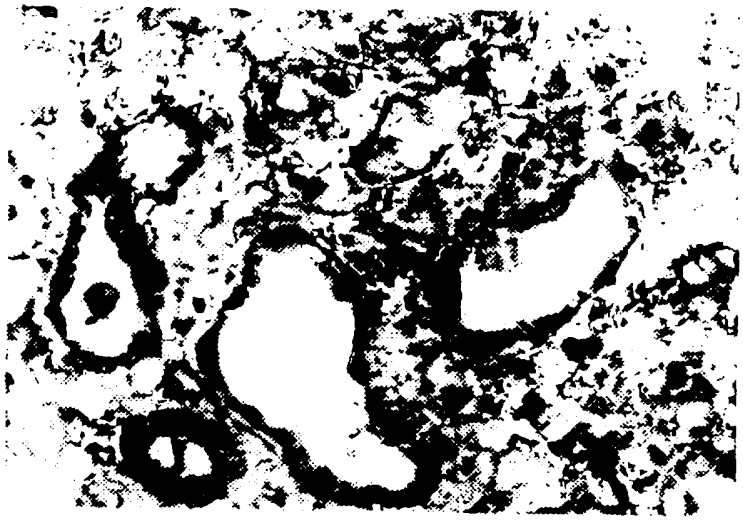

FIGURE 3A

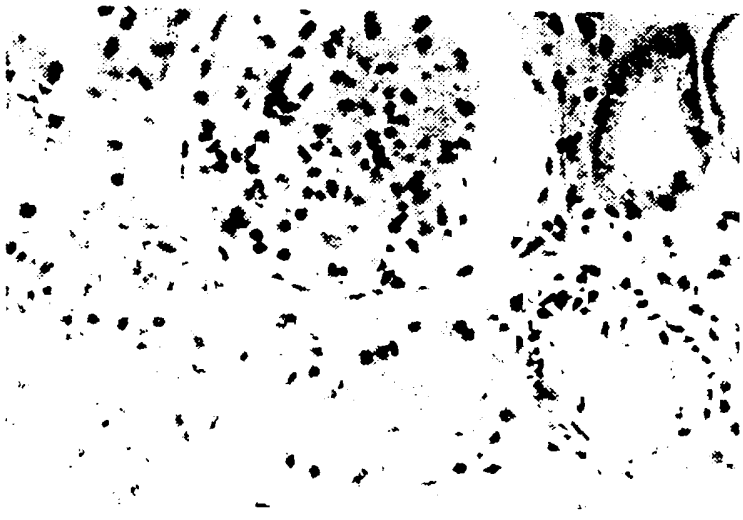

FIGURE 4A

FIGURE 4B

FIGURE 5

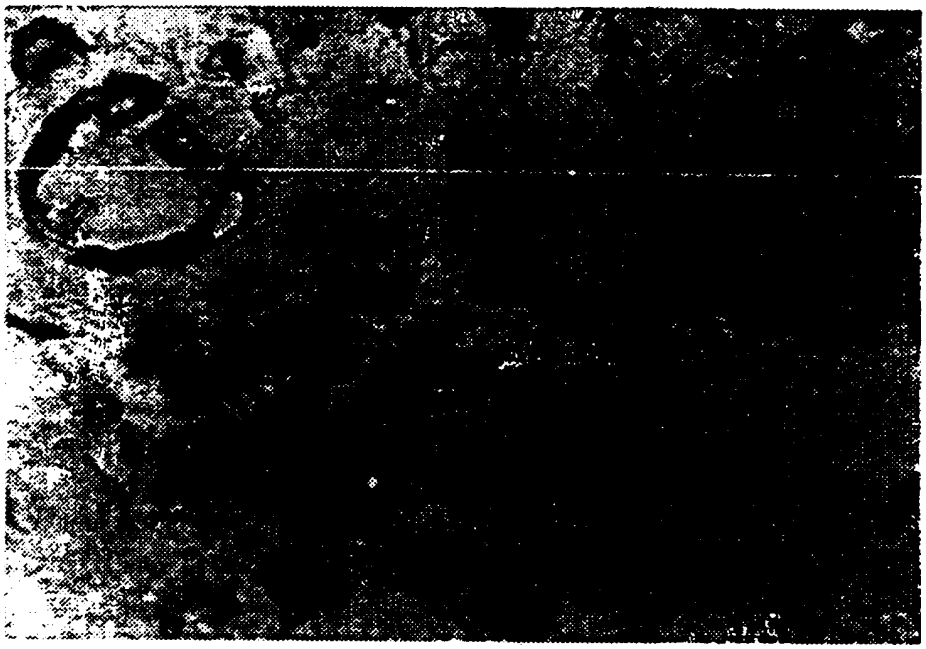

FIGURE 6

FIGURE 7

FIGURE 8

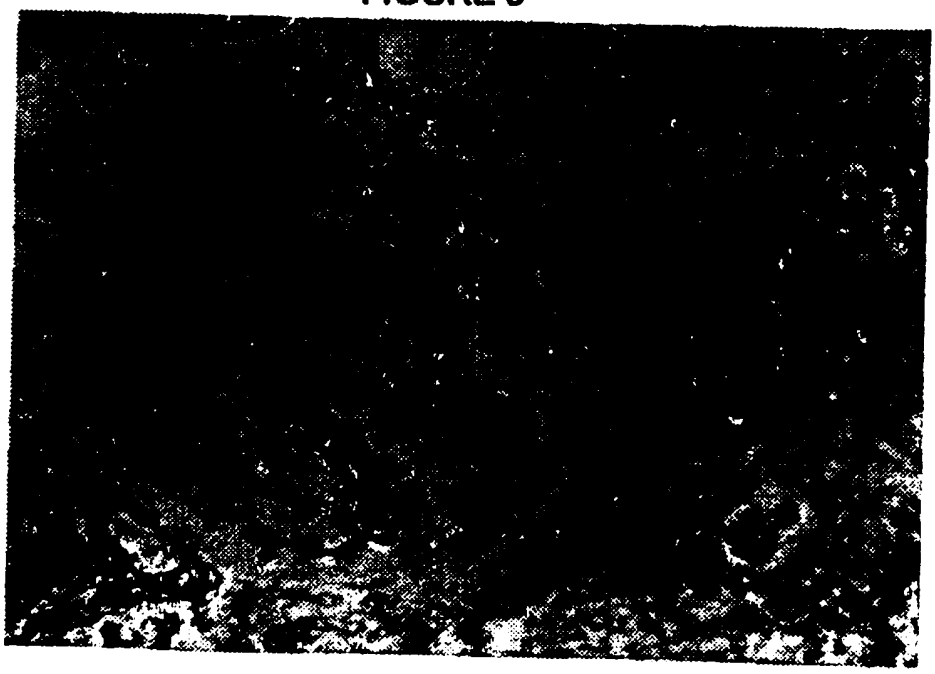

FIGURE 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/00668

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/02, 38/17; 39/395
US CL :424/130.1, 133.1, 141.1, 144.1, , 154.1, 173.1; 514/2, 8
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/130.1, 133.1, 141.1, 144.1, , 154.1, 173.1; 514/2, 8

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, DIALOG, BIOSIS, CA, EMBASE, MEDLINE, WPI
search terms: 5c8, cd40L, cd40 ligand, kidney, renal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 93/09812 A1 (THE TRUSTEES OF COLUMBIA UNIESTIY IN THE CITY OF NEW YORK) 27 MAY 1993, see entire document.	1-23, 31-57, 65-76 --- 24-30, 58-64
X --- Y	Kidney International, Volume 48, issued 1995, Biancone et al., "Inhibition of the CD40-CD40 ligand pathway prevents murine membranous glomerulonephritis", pages 458-468, see entire document.	1-23, 31-57, 65-76 --- 24-30, 58-64
Y	Structure, Volume 3, issued 15 October 1995, Karpusas et al., "2 A crystal structure of an extracellular fragment of human CD40 ligand", pages 1031-1039, see entire document.	1-76

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 01 MAY 1997	Date of mailing of the international search report 02 JUN 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PHILLIP GAMBEL Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/00668

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Science, Volume 257, issued 21 August 1992, Kuntz et al., "Structure-Based Strategies for Drug Design and Discovery", pages 1078-1082, see entire document.	1-76